Clinicoradiologic follow up of cherubism with aggressive characteristics: a series of 3 cases

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Cherubism is a rare autosomal dominant disorder characterized by replacement of bone with fibrous tissue containing multinucleated giant cells. It manifests as bilateral mandibular and/or maxillary enlargement. The 2017 World Health Organization classification lists cherubism as a giant cell lesion of the jaws, distinct from fibro-osseous disorders. We discuss 3 cases of familial cherubism having aggressive characteristics and present clinicoradiologic evaluations of the lesions over 12, 18, and 1.5 years, respectively. Follow-up was observational, without active intervention. Analysis of the lesions for change in size and functional impairments was correlated with periodic imaging. All patients are currently being monitored. The outcome in 2 cases has been excellent without intervention, but 1 case had extensive involvement of the jaws and involvement of the condyle and orbit. A secondary giant cell lesion involved the palate in one patient's mother, who had had cherubic lesions in childhood. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:e191–e201)

Cherubism (Online Mendelian Inheritance in Man: 118400) is a rare, htt inherited disease of children that is characterized by bilateral painless mandibular and often maxillary enlargement, resulting in fullness of cheeks, intraoral alveolar swelling, and displaced or unerupted teeth, often resembling the depiction of cherubs in Renaissance art.[1] Cherubism was first described in 1933 by Jones as "familial multilocular disease of the jaws," but the term "cherubism" was later coined to describe the rounded facial appearance resulting from jaw enlargement.[2] According to the World Health Organization (WHO, 1971), cherubism belongs to a group of nonneoplastic bone lesions that affect only the jaws. It belongs to the spectrum of fibro-osseous diseases.[3] The recent 2017 WHO classification now lists cherubism as one of the giant cell lesions of the jaws, distinct from fibro-osseous disorders. Several grading systems exist for the classification of cherubism.[4] The first grading system was suggested by Fordyce in 1976 and defined by Arnott[5] as follows:

Grade 1—fibro-osseous bilateral and symmetric expansions in the rami of the mandible

Grade 2—more severe involvement of the ramus and body of the mandible and the tuberosity region of the maxillae

Grade 3—involvement of maxillae and mandible in their entirety with considerable facial deformity

Cherubism has been classified according to severity by Motamedi in 1998 and later modified by Raposo-Amaral in 2007.[6,7] Motamedi[6] proposed a grading system with 5 grades on the basis of both the aggressiveness of the disease and the jaws involved. These grades are further divided into classes to denote the sites and the numbers of lesions. The subclasses designate condylar or coronoid involvement. Motamedi's grading system was later modified by Raposo-Amaral by the addition of the sixth grade to describe involvement of the orbit.[7]

Statement of Clinical Relevance

No surgical intervention is required in most of cases of cherubism because the lesions show spontaneous involution. Long-term clinical and radiologic assessment should be done to evaluate the lesions and detect development of any secondary giant cell lesion in the later phases of life.

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On the basis of clinical behavior and radiographic findings, cherubism has been characterized as quiescent, nonaggressive, and aggressive.[8] Quiescent cherubic lesions are common in older age groups and do not demonstrate progressive growth, whereas nonaggressive lesions are most frequently present in teenagers. Lesions in the aggressive form of cherubism are found in young children and grow rapidly. They may cause tooth displacement, root resorption, and thinning and perforation of cortical bone, leaving only a fenestrated shell of cortical bone.[8]

The characteristic feature of cherubism is the development of symmetric, expansile, bony enlargement that usually becomes evident at age 2 to 7 years. It commonly involves the mandible, but the maxillae may also be affected.[1,3] The lesions typically progress until puberty and thereafter may undergo spontaneous resolution. However, the severity of the phenotypic manifestation is highly variable because of variable penetrance and expression, even within a family.[8] This condition is primarily characterized as familial, but sporadic cases have also been reported.[3] Most of the cases present as an autosomal dominant trait or with de novo mutations. Penetrance in males and in females is equal. Mutations in the *SH3BP2* gene are identified in 80% of cases of cherubism.[9,10]

There are various proposed treatment modalities, including resection or curettage, along with bone contouring and nonsurgical methods, such as systemic calcitonin, intralesional steroid injections, and subcutaneous administration of interferon-α.[11] Each treatment has its own risks for unpredictable outcomes. At present, there is no cure for this condition, and there are very specific indications for surgical intervention, which is not performed except in cases with significant functional, aesthetic, or emotional disturbances.

The choice between conservative management and surgical management is vital, as cherubic lesions spontaneously regress at variable time intervals. Because of orofacial disfigurement, patients suffer psychological distress as well as reduced quality of life. Therefore, there is an urgent need for multidisciplinary management strategies. The ultimate goals include restoring stomatognathic function and aesthetic rehabilitation, as well as improved quality of life with reduced social stigma, while avoiding life-threatening complications, such as respiratory distress. Therefore, an improved understanding of the long-term behavior of the disease is required to obtain better outcomes.[12] The literature states that osseous repair has been observed radiographically in patients over a period. In adult life, patients often exhibit a return of normal facial contours with almost complete involution of the lesions.[13] Long-term follow-up of such patients is necessary to evaluate progression or involution of the lesions; therefore, a "wait and watch" approach was applied to our cases. Studies of cherubism with long-term follow-up clearly demonstrating spontaneous resolution of lesions are scarce in the literature.[12] We report 3 patients diagnosed with familial cherubism, with long-term follow-up of 2 of the patients. Clinical and radiographic findings highlight the involution of the lesions in the absence of active intervention. Another important finding was the development of a secondary giant cell lesion involving the palate in the mother of one of the patients.

CASE 1

This case is documented with extraoral and intraoral photographs (Figures 1A through 1I), a photomicrograph (Figure 2), axially reformatted computed tomography (CT) scans (Figures 3A through 3F), and 3-dimensional CT reconstructions (Figures 4A through 4I). A 5-year-old female was brought to the Department of Oral Medicine and Radiology with painless bilateral enlargement of the face. Her parents said that she was apparently normal until age 1.5 years (see Figure 1A), after which time they noticed facial asymmetry with enlargement of both sides of the face that was gradually increasing in size. The family history revealed that the patient's mother had had mandibular asymmetry in childhood that was later recontoured, but her father and an older brother had no evidence of any such disease.

On extraoral examination, bilateral bony hard enlargement involving the mandible and the maxillae was present, with the overlying skin normal in color and texture at various times from age 5 to 18 years (see Figures 1B through 1H). Intraorally, there was bony hard expansion of the alveolar mucosa in the mandibular and maxillary arches with multiple missing teeth (see Figure 1I). Axial CT examination at age 5 years revealed bilateral, multilocular osteolytic lesions in the mandible and the maxilla, with expansion and thinning of the cortical plates. Laboratory tests revealed normal calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels. After correlating the history, clinical findings, and radiographic features, a provisional diagnosis of familial cherubism was made. Incisional biopsy from the mandibular lesion was performed, and histopathologic examination revealed numerous equidistantly placed giant cells with 10 to 15 round nuclei, interspersed with fibrous stroma and scanty numbers of irregular bony trabeculae. These features were suggestive of a giant cell lesion (see Figure 2). Genetic analysis of the affected members of the family revealed a missense mutation (c.1258 G>A; *P*.Gly420Arg) in exon 9 of the *SH3BP2* gene in the

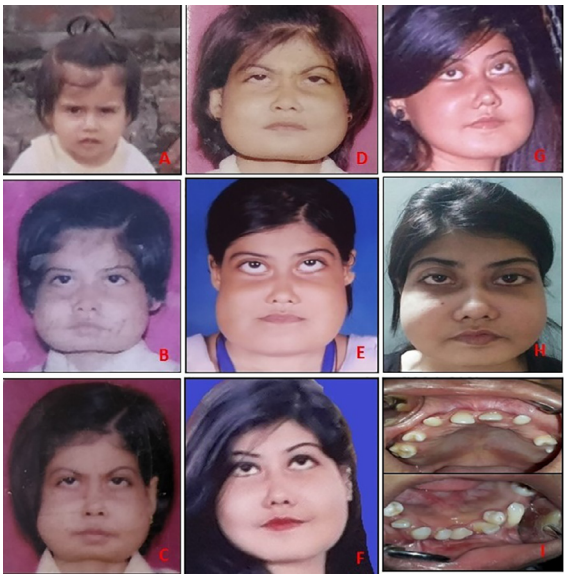

Fig. 1. **Case 1. (A)** Extraoral photograph showing no obvious jaw enlargement at 1.5 years. **(B)** Extraoral photograph showing symmetric bony hard expansion involving bilateral maxillary and mandibular regions at 5 years. **(C)** Extraoral photograph showing slight increase in enlargement involving the bilateral maxillae and mandible at 6 years. **(D)** Extraoral photograph showing further increase in symmetric bilateral facial enlargement at 8 years. **(E)** Extraoral photograph showing enormous deformity involving the bilateral maxillae and the mandible with the classic cherubic face. The irises of the eyes are displaced upward, leaving visible sclera at 11 years. **(F)** Extraoral photograph showing regression of maxillary and mandibular lesions at 15 years. **(G)** Extraoral photograph showing significant regression of maxillary and mandibular enlargement at 16 years. **(H)** Extraoral photograph showing further significant regression of the maxillary and mandibular lesions and eyes showing normal positioning of irises and sclera at 18 years. **(I)** Intraoral photographs showing multiple unerupted and displaced teeth with microdontia in the maxillae and the mandible.

patient and in her mother.[14] The patient and her family were given counseling regarding this disorder, and it was decided to keep the patient under regular follow-up to observe the behavior of the lesion, but without any intervention.

The size of the bilateral mandibular and maxillary expansion gradually increased, as documented on subsequent visits and shown in Figures 1C and 1D at ages 6 years and 8 years, respectively.

At age 11 years, the maximum progression of the lesions involving the mandible and the maxillae produced the classic Renaissance cherubic face (see Figure 1E). Bilateral orbital involvement was also seen, with the irises displaced superiorly, leaving below the exposed sclera—the characteristic sign of eye involvement in cherubism. The patient frequently complained of episodic headache. Axial noncontrast

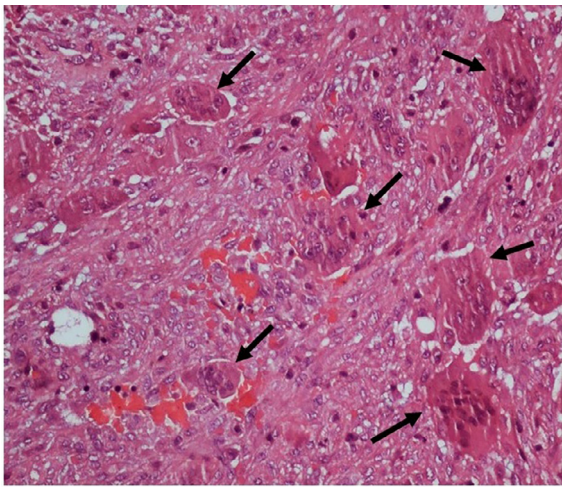

Fig. 2. **Case 1.** Histologic microphotograph showing numerous multinucleated giant cells *(shown by arrows)* interspersed in fibroblastic stroma (hematoxylin and eosin, × 200).

computed tomography (NCCT) sections were exposed at ages 11, 16, and 18 years (see Figures 3A through 3F), and 3-dimensional (3D) reconstructions were produced (see Figures 4A through 4I). Extensive, bilateral multilocular osteolytic lesions involving the entire mandible and multiple impacted and displaced teeth

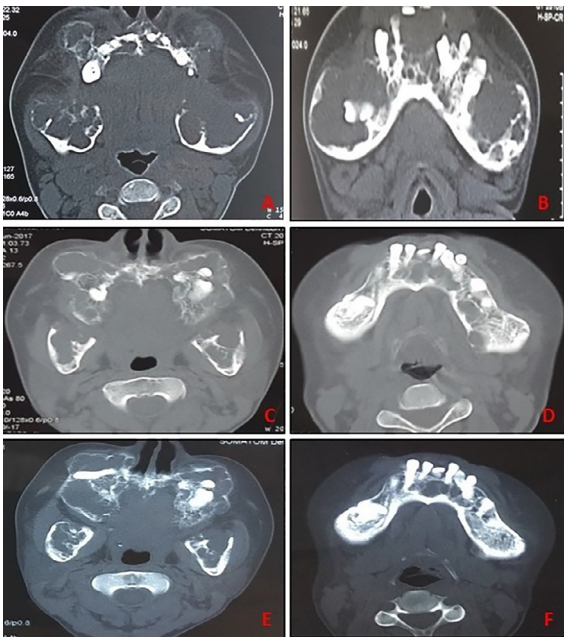

Fig. 3. **Case 1. (A), (B)** Axial computed tomography (CT) sections showing extensive, expansile bilateral multilocular osteolytic lesions of the maxillae and mandible with expanded cortices and multiple impacted and displaced teeth at 11 years. **(C), (D)** Axial CT sections showing regression and remodeling of lesions involving the mandible and maxillae at 16 years. **(E), (F)** Axial CT sections showing significant amount of bony remodeling, with new bone formation appearing as a ground-glass matrix and regression at 18 years.

were detected age 11 years (see Figures 3A and 3B). There was almost complete obliteration of the bilateral maxillary sinuses, with the lesion causing superior bulging of the inferior walls of bilateral orbits. NCCT 3D reconstruction confirmed massive, multilocular osteolytic lesions involving the most of the mandibular and maxillary bones with encroachment of bilateral orbits (see Figures 4A and 4B). The osteolytic lesion also involved the right mandibular condyle, but the left condyle was spared (see Figure 4C).

The extraoral and intraoral expansion gradually diminished in size after 12 years of age. Clinically, there was significant regression in the enlargement bilaterally over the face involving the mandible and maxillae at age 15 years (see Figure 1F). There was also improvement in both orbits, with slight downward positioning of the irises.

At age 16 years, there was further significant remission in the cherubic enlargement involving the bilateral mandible and maxillae (see Figure 1G). Axial NCCT sections revealed expansile lytic lesions in both jaws, with coarsened trabeculae and areas of ground-glass matrix (see Figures 3C and 3D). There was associated thinning of the overlying cortices. NCCT 3D reconstruction showed substantial involution of the lesions and replacement of significant amounts of the lesion with bone formation (see Figures 4D, 4E, and 4F).

At age 18 years, there was further reduction in the facial deformity on both sides involving the mandible and the maxillae. Bilaterally, the orbits appeared normal with respect to the position of the irises and the sclerae (see Figure 1H). Intraoral photographs revealed displaced teeth with generalized microdontia in the maxillary and mandibular arches along with multiple impacted teeth (see Figure 1I). Axial NCCT sections revealed expansile lytic lesions containing a ground-glass matrix, along with remodeling of the cortices in the jaws (see Figures 3E and 3F). NCCT 3D reconstruction revealed considerable replacement of osteolytic lesions with the remodeled new bone. Normal contouring had been regained over this period (see Figures 4G, 4H, and 4I).

The mandibular lesions had undergone significant regression, but the maxillary lesions were still prominent. Because of cosmetic concerns of the patient, surgical debulking of the lesion has been planned. The patient is still under regular follow-up.

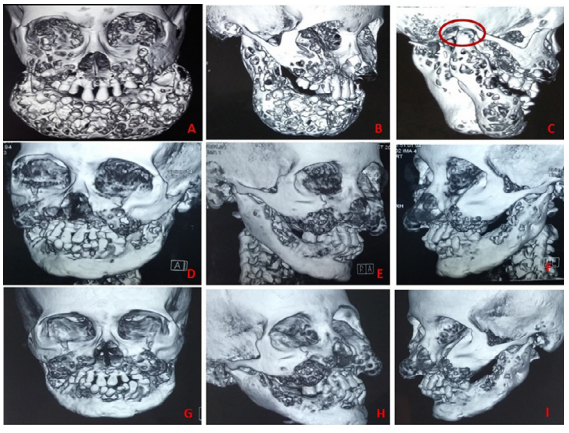

Fig. 4. **Case 1. (A), (B), (C)** Three-dimensional computed tomography (3D CT) reconstruction showing bilateral multilocular osteolytic lesions involving the maxillae and the mandible with expanded cortices, maxillary lesions extending to the orbit, and lytic lesion in the right mandibular condyle *(circle)* at 11 years. **(D), (E), (F)** 3D CT reconstruction (frontal and lateral) showing regression and remodeling of lesions involving the mandible and maxillae at 16 years. **(G), (H), (I)**, 3D CT reconstruction (frontal and lateral) showing a significant amount of bony remodeling, with new bone formation. The orbits appear normal (age 18 years).

Secondary giant cell lesion in the patient's mother

The patient's mother reported with a complaint of palatal enlargement that had been progressing over the past 1 year. She had had cherubic lesions involving the mandible in her childhood, but the mandible was almost completely remodeled at the time she reported for the palatal swelling. On examination, there was firm to hard exophytic lesion of approximately 1×1 cm in the midline of the hard palate, with the overlying mucosa blue to brown in color and nontender on palpation (Figure 5A). Coronal NCCT sections revealed a soft tissue lesion of 0.5×0.6 cm in the region of the hard palate on the right side with a defect in the overlying bony hard palate (Figure 5B). Fine-needle aspiration cytology (FNAC) from the palatal swelling showed a number of osteoclastic giant cells, along with occasional scattered spindle cells and scant to moderate cytoplasm in a hemorrhagic background. These features were suggestive of giant cell−rich lesion.

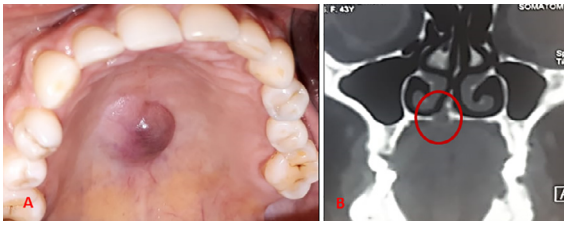

Fig. 5. **(A)** Intraoral photograph showing palatal enlargement manifesting as a secondary giant cell lesion in patient 1's mother, who had a history of cherubism. **(B)** Coronal noncontrast computed tomography (NCCT) section showing a soft tissue lesion with erosion of the overlying hard palate on the right side *(circle)*.

CASE 2

This case is documented with extraoral photographs (Figures 6A through 6F), FNAC (Figure 7), panoramic radiography (Figures 8A through 8C), and CT in 2-dimensional (2D) (Figures 8D and 8E) and 3D reconstructions (Figures 8F through 8H). A 5-year-old male was brought with painless, enlargement of the lower jaw progressing since age 3 years. His parents had noticed a change in facial symmetry that had gradually become more obvious. Family history revealed that the presence of enlargement in the father's lower jaw in his childhood, which had subsequently regressed. Screening of the patient's father with panoramic radiography revealed a rarefaction, with alteration in the normal bony trabecular pattern suggestive of bilaterally remodeled areas in the mandibular body. Genetic analysis could not be performed in this family.

In the patient, extraoral enlargement was evident over the bilateral posterior mandibular region. The enlargement was bony hard and nontender and was more prominent on the right side (see Figure 6A). Intraorally, expansion of the mandibular alveolar ridge was present in the posterior region. Laboratory tests showed normal calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels. FNAC of the right mandibular area showed scant cellularity, with predominantly multinucleated giant cells in a hemorrhagic background and interspersed with dispersed

Fig. 6. **Case 2. (A)** Extraoral photograph showing facial asymmetry, with mandibular enlargement on the right side at 5 years. **(B)** Extraoral photograph showing bilateral mandibular lesions that are more prominent on the right side, with normal-appearing bilateral orbits at 8 years. **(C)** Extraoral photograph showing increase in mandibular enlargement on the right side at 10 years. **(D)** Extraoral photograph showing the maximum increase in mandibular expansion on the right side, with no involvement of the orbits at 13 years. **(E)** Extraoral photograph showing regression in the mandibular lesion on the right side at 21 years. **(F)** Extraoral photograph showing significant regression in mandibular enlargement on the right side at 23 years.

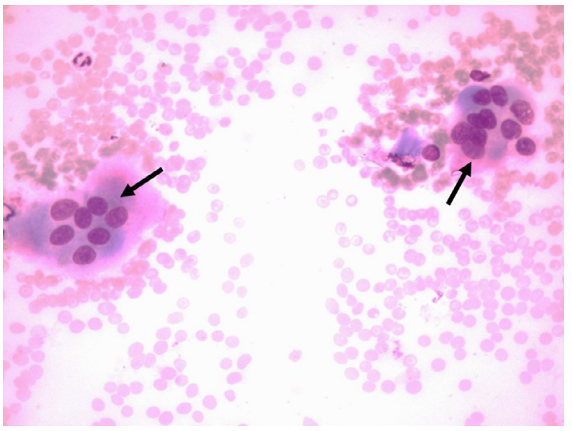

Fig. 7. **Case 2.** Fine-needle aspiration cytology (FNAC) from the jaw lesion showing scanty cellularity with predominant multinucleated giant cells *(shown by arrows)*.

fibroblasts. These features were suggestive of a giant cell lesion (see Figure 7). On correlating the findings from history, clinical examination, and investigation reports, the diagnosis of familial cherubism was made. The mandibular deformity gradually increased with age. Periodic follow-up was undertaken, without active intervention. The patient and his parents were made

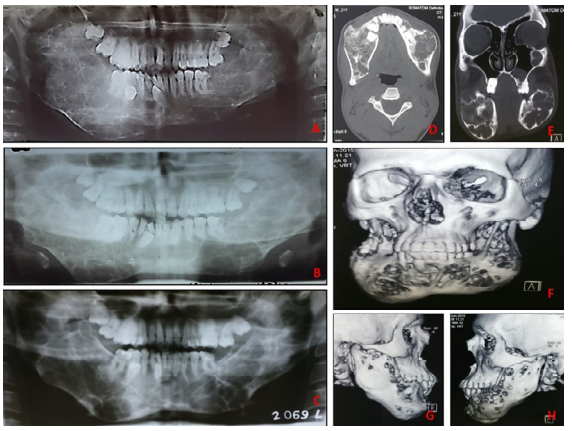

Fig. 8. **Case 2. (A)** Panoramic radiograph showing bilateral multilocular, osteolytic lesions involving the mandible with a thinned and expanded cortex, no involvement of the condyle bilaterally, developing teeth 1, 16, and impacted 27, 29 at 13 years. **(B)** Panoramic radiograph showing bilateral osteolytic lesions involving the mandible with expanded cortex at 15 years. **(C)** Panoramic radiograph showing significant regression and remodeling of involved bone with patchy areas of ground-glass appearance at 23 years. **(D), (E)** Axial and coronal computed tomography (CT) section showing significant remodeling of mandibular bone with patchy areas of ground-glass appearance, also seen in the lateral wall of the left maxillary antrum at 21 years. **(F), (G), (H)** Three-dimensional (3D) CT reconstruction (frontal and lateral) showing a small osteolytic multilocular lesion along with remodeling of new bone in the mandible but no evidence of condylar involvement bilaterally at 21 years.

aware of this disorder and counseled regarding its hereditary nature.

When the patient was 8 years of age, there was an increase in the size of the bony hard lesion bilaterally in the mandibular body, but more prominently on the right side (see Figure 6B). The overlying skin was normal in color and texture. There was no evidence of expansion involving the maxillae. There was no orbital involvement, with normal irises and sclerae bilaterally.

At age 10 years, there was further increase in mandibular expansion, predominantly on the right side, causing more facial asymmetry (see Figure 6C). The overlying skin was normal. There was no maxillary enlargement or orbital involvement. The dentition was also becoming crowded, as observed in subsequent follow-ups.

At age 13 years, maximum deformity was seen involving the mandible, predominantly on the right side, with a slight increase in enlargement on the left side (see Figure 6D). The skin overlying the deformed areas appeared normal. There was no evidence of maxillary enlargement or orbital involvement. Panoramic radiography revealed bilateral multilocular, osteolytic lesions involving the mandible, with thinned and expanded cortices. There was no involvement of the mandibular condyles. There was evidence of developing maxillary right and left third molars and impaction of the right mandibular canine and second premolar at age 13 years (see Figure 8A). Panoramic radiography at age 15 years was similar, with slight resolution of the lesions and expansion of the inferior border of the mandible (see Figure 8B).

At age 21 years, there was regression in the mandibular lesion, more prominently on the right side (see Figure 6E). Axial and coronal NCCT revealed expansile lytic lesions interspersed with areas of ground-glass matrix and remodeling of the cortices in mandible. Similar remodeling was noted in lateral wall of left maxillary antrum and left alveolar process of maxilla (see Figures 8D and 8E). NCCT 3D reconstruction revealed considerable replacement of the osteolytic lesions in the mandible with remodeled new bone. A return to normal contour was noted. There was no involvement of the mandibular condyles (see Figures 8F, 8G, and 8H).

At age 23 years, further involution of the mandibular lesion was detected on the right side and almost complete resolution of the lesion on the left side (see Figure 6F). Panoramic radiography showed significant remodeling of the involved bone, with patchy ground-glass areas in the mandible (see Figure 8C). The patient is still under periodic follow-up.

CASE 3

This case is documented with photographs, panoramic radiography, and CT (Figures 9A through 9K). A 3-year-old male was presented with slowly enlarging, painless, symmetric deformity of the face, along with multiple unerupted teeth. When the child was 1.5 years of age, the parents had noticed a change in facial symmetry, which later became more obvious. His father and older brother had no such problems, but his mother gave a history of a similar enlargement of her face in childhood that had regressed spontaneously. Panoramic radiography revealed multiple osteolytic lesions in the mandible, along with multiple unerupted teeth (see Figures 9A, 9B, and 9C).

On extraoral examination, bilateral bony hard enlargement of bilateral maxillae and the mandible with normal overlying skin was observed (see Figure 9D). Bilateral submandibular lymph nodes were palpable, mobile, and nontender. Intraoral examination revealed expansion of the maxillary and mandibular

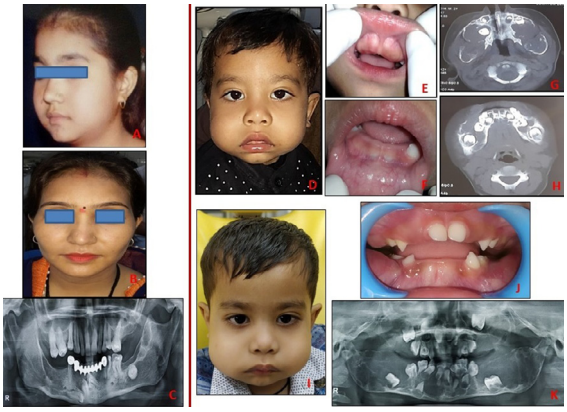

Fig. 9. **Case 3.** **(A)** Extraoral photograph showing symmetric bilateral mandibular deformity in the patient's mother in her childhood. **(B)** Extraoral photograph of the patient's mother showing no evidence of any mandibular enlargement when she presented to us with her 3-year-old son. **(C)** Panoramic radiograph showing multiple osteolytic lesions involving the left mandibular ramus and the left and right mandibular body with multiple impacted teeth. **(D)** Extraoral photograph showing bilateral enlargement of the maxillae and the mandible at 3 years. **(E), (F)** Intraoral photographs showing unerupted primary teeth at 3 years. **(G), (H)** Axial computed tomography (CT) sections showing bilateral multilocular osteolytic lesions with cortical expansion involving the maxillae and the mandible at 3 years. **(I)** Extraoral photograph showing increase in mandibular and maxillary enlargement at 4.5 years. **(J)** Intraoral photographs showing eruption of primary teeth at 4.5 years and bony hard swelling in the bilateral mandibular posterior vestibular region. **(K)** Panoramic radiograph showing multiple osteolytic lesions involving the maxillae and the mandible, as well as the mandibular condyle bilaterally, with multiple impacted and displaced teeth at 4.5 years.

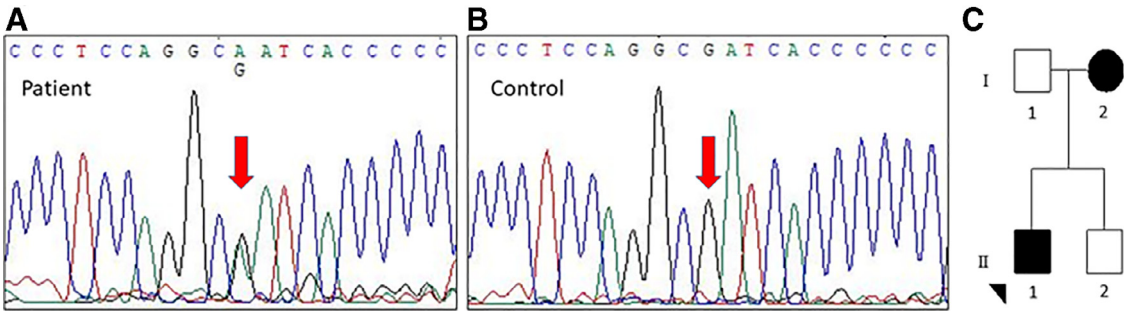

Fig. 10. **Case 3. (A), (B), (C)** Genetic analysis of the family of case 3 showing the electropherograms of the heterozygous *SH3BP2* gene mutation in exon 9 (c.1244G>A, *P*.415R>Q) for the proband (II-1) and his affected mother (I-2) and the normal sequence for the unaffected sibling (II-2) and his unaffected father (I-1). Electropherogram: Colored lines represent nucleotides: T = red; G = black; A = green; and C = blue. Red arrow indicates heterozygous mutation in the proband **(A)** and the position of the normal nucleotide in the control **(B)**. Pedigree **(C)**: Circle represents female, square represents male; filled symbols are family members affected by cherubism in generation I and in generation II.

alveolar ridges. Only the deciduous maxillary and mandibular first molars and the left mandibular canine had erupted; the other primary teeth were missing (see Figures 9E and 9F). Laboratory investigations showed elevated alkaline phosphatase level (270 IU/L) but normal serum calcium, phosphorus, and parathyroid hormone levels. Axial CT revealed well-defined, multilocular, bilateral expansile maxillary and mandibular lesions with multiple unerupted and displaced teeth (see Figures 9G and 9H). FNAC of the mandibular swelling showed predominantly multinucleated giant cells with dispersed fibroblasts. These features were suggestive of a giant cell lesion. Correlating the findings from history, clinical examination, and investigation reports, the diagnosis of familial cherubism was made. Genetic analysis was performed for the patient, his affected mother, and his unaffected brother and father. Mutation analysis revealed a missense mutation in exon 9 (c.1244G>A; *P*.415R>Q) changing arginine at position 415 to glutamine of *SH3BP2* in the patient and his mother, confirming familial cherubism (Figure 10). Counseling was provided to the family regarding this genetic disorder.

At age 4.5 years, increased extraoral maxillary and mandibular enlargement was noticed (see Figure 9I) coinciding with the eruption of the maxillary central incisors and bilateral maxillary canines (see Figure 9J). Panoramic radiography revealed bilateral, multilocular, osteolytic lesions involving the mandible and the maxillae with multiple impacted teeth. The right and left condyles were also involved (see Figure 9K).

DISCUSSION

Clinical manifestations of cherubism range from insignificant lesions that often go undiagnosed or diagnosed as an incidental finding related to aggressive lesions involving both jaws, causing substantial bony destruction and facial deformity. This is illustrated in the present cases. Patient 1 experienced massive destruction of the mandible and the maxilla, resulting in significant facial deformity, but the patient 2 had only mandibular involvement. Most patients are normal at birth. Cherubism arises in the first decade, usually in the second or third year of life. The Motamedi[6] system of grading addressed both the involvement and the aggression of the disease by classifying cherubism into 5 grades, which are further divided into classes:

Grade I: Lesions of the mandible without signs of root resorption:

- Class 1: Solitary lesion of the mandibular body
- Class 2: Multiple lesions of the mandibular body
- Class 3: Solitary lesion of the ramus
- Class 4: Multiple lesions of the rami
- Class 5: Lesions involving the mandibular body and rami

Grade II: Lesions involving the mandible and maxilla without signs of root resorption:

- Class1: Lesions involving the mandible and maxillary tuberosities
- Class 2: Lesions Involving the mandible and anterior maxilla
- Class 3: Lesions involving the mandible and entire maxilla

Grade III: Aggressive lesions of the mandible with signs of root resorption:

- Class 1: Solitary lesion of the mandibular body
- Class 2: Multiple lesions of the mandibular body
- Class 3: Solitary lesion of the ramus

- Class 4: Multiple lesions of the mandibular rami
- Class 5: Lesions involving the mandibular body and rami

Grade IV: Lesions involving the mandible and maxillae and showing signs of root resorption:

- Class 1: Lesions involving the mandible and maxillary tuberosity
- Class 2: Lesions involving the mandible and anterior maxilla
- Class 3: Lesions involving the mandible and entire maxilla

Grade V: The rare, massively growing, aggressive, and extensively deforming lesion in juvenile cases, involving the maxilla and the mandible, and may include the coronoid and condyles.

Grade VI: The rare, massively growing, aggressive, and extensively deforming lesion in juvenile cases, involving the maxilla, the mandible, and the orbits. (Modified by Raposo-Amaral et al.[7])

Papadaki et al. suggested the necessity for a clinician to differentiate aggressive lesions from nonaggressive lesions on the basis of rate of growth, size, cortical bone perforation or thinning, tooth displacement, and the functional deficits.[8] Chuong et al. also stated that the biologic behavior of central giant cell lesions of the jaws ranges from quiescent to aggressive with destructive expansion.[15] They described the following clinical criteria for giant cell lesions of the jaws to distinguish between aggressive and nonaggressive lesions[15]:

- Pain—present in aggressive lesions and not present in nonaggressive lesions
- Rate of growth—rapid in aggressive lesions and slow in nonaggressive lesions
- Swelling—large in aggressive lesions and variable in nonaggressive lesions
- Root resorption—often present in aggressive lesions and not present in nonaggressive lesions.
- Cortical perforation—often present in aggressive lesions and variable in nonaggressive lesions.
- Recurrence—present in aggressive lesions and not present in non-aggressive lesions

The pathophysiology of cherubism includes mutations in the gene encoding SH3-binding protein SH3BP2 on chromosome 4p16.3. The overactive SH3BP2 protein triggers the production of osteoclasts in the jaws, leading to bone resorption, followed by fibrous tissue replacement.[16] It was shown in mice that these mutations result in increased production of tumor necrosis factor-α, which further induces inflammatory reaction, bony destruction, and increased osteoclast formation.[16,17] Kadlub et al.[18] stated that multinucleated giant cells in cherubism are CD68-positive cells, which differentiate into macrophages in nonaggressive cherubism and into osteoclasts in aggressive cherubism, stimulated by the NFATc1 pathway. In cases 1 and 3, the patients' mothers had a mutation in the *SH3BP2* gene; however, in case 2, the inheritance was from the father. Moreover, the severity of phenotypic expression was highly variable in the family of case 1, revealing very aggressive behavior of the lesion, causing huge facial deformity, whereas the patient's mother showed nonaggressive quiescent lesions. There have been nearly 25 case reports from India describing the clinical, radiologic, and histologic phenotypes of cherubism, but none of them was confirmed through genetic testing.[14]

Clinically, this condition mainly affects the mandible and the maxillae bilaterally. However, Holley et al.[19] demonstrated a unique presentation of unilateral cherubism that eventually involved the contralateral side. Ocular involvement typically presents with retrusion of the lower eyelid and exposure of the sclera below the pupil resembling the "Renaissance portrayals of angels."[20] Case 1 showed all of these typical features, whereas case 2 had predominantly mandibular involvement. The most severe lesions may affect deglutition, swallowing, breathing, and speech.[20]

Various dental alterations are also found concomitant with cherubism. They vary in time of onset and severity of the expansile bony lesions and can manifest as early exfoliation of primary teeth, as well as dental impaction and displacement. Ectopic eruption and agenesis of permanent teeth, commonly the second and third molars, have been observed. These alterations can result in malocclusion as well as in problems of phonation and swallowing.[8] The patient in case 1 had multiple impacted permanent teeth, hypodontia, displaced teeth, and generalized microdontia caused by aggressive lesions. However, such severe dental alterations were not observed in case 2. Therefore, we can conclude that more aggressive lesions at early age cause more dental alterations.

Cherubism is usually limited to the mandible and the maxilla, but there are only rare reports of involvement of the mandibular condyles. This may result from the greater quantity of compact bone and few marrow spaces, making condylar invasion difficult.[20] Only 3 cases with condylar involvement have been reported.[21-23] The present case study revealed involvement of mandibular condyle in cases 1 and 3. Extracranial involvement is very rare, with 3 reports in the

literature regarding involvement of ribs in cherubism.[24-26] Cherubism is usually an isolated finding. However, various syndromes are associated with the disease. These include neurofibromatosis type I, Noonan-like/multiple giant cell lesion syndrome, Ramon syndrome, and Jaffe-Campanacci syndrome.[8] In our cases, complete examination and screening ruled out extracranial involvement as well as any other syndromic conditions.

Some patients with severe manifestations of cherubism complain of episodic pain and headache,[27] and this was consistent with case 1. In more severe forms of cherubism, the lesion extends into the inferior and/or lateral orbital wall. This can cause physical displacement of the globe and retraction of the eyelids, resulting in exposure of the sclera beneath the iris. Cherubism lesions may also invade the retrobulbar spaces of the orbits and cause displacement of the optic nerves and proptosis.[28] This upward gaze and proptosis was more prominently observed in case 1 as the lesions aggressively extended into the orbits. Colombo et al. reported that orbital involvement in cherubism may develop beyond puberty, after stabilization or regression of the lesions in the jaws.[28] Font et al. described a patient who had a 27-year history of cherubism and experienced reduced mobility of the eyes. CT revealed bilateral inferior lateral masses in the orbital floors, producing marked superior displacement of the orbital contents. Intrinsic expansile bone lesions involved the inferior and lateral orbital walls with apical compression of the optic nerves.[29] For this reason, patients with cherubism and maxillary involvement should be kept under regular ophthalmologic supervision to avoid any complications.

Respiratory problems may manifest as upper airway obstruction because of backward displacement of the tongue or nasal airway obliteration. This may lead to mouth breathing, snoring, chronic nasal infection, and obstructive sleep apnea.[30] In such cases, surgical intervention may be necessary. None of the patients in this case series had respiratory involvement.

Laboratory tests help in the characterization of the disease because hematologic parameters, such as calcium and phosphorus levels, are usually normal and only alkaline phosphatase levels might be elevated. Lima et al. stated that the increase in alkaline phosphatase can be explained by the developmental phase of disease.[31] However, some authors have stated that cherubism does not involve extragnathic bones, and biochemical bone markers, such as calcium, phosphorus, and alkaline phosphatase levels, have been found within the normal range for the patients' age.[20] Cases 1 and 2 showed normal serum chemistry, but the patient in case 3 had an increased level of serum alkaline phosphatase.

In cherubism, the obvious concern of patients and their families is the facial disfigurement, which has a significant association with social stigma as well. Another consideration is the possibility of genetic transmission to future generations.[8] Considering the psychosocial factors and quality of life issues, counseling was provided to the patients and their families in cases 1, 2, and 3 through explanation of the nature of disease, its progression, its effect on adjacent structures, and its characteristic self-involution and regression after puberty. One proposed hypothesis for self-involution of cherubism is that plasma concentrations of estrogen and testosterone increase drastically at puberty; these sex hormones are known to inhibit osteoclast formation.[20] The condition begins to regress around puberty and continues until 30 years of age. Therefore, a "wait and watch" approach was preferred in all of the present cases. Long-term follow-up periods were 12 years and 18 years for cases 1 and 2, where the jaws were extensively involved before puberty. The lesions are now under regression with progressive new bone formation as well as significant reduction in jaw enlargement.

There is no standard treatment protocol for cherubism, but the indications for treatment should be based on the rate of lesion progression, the extent of its involvement, and the emotional state of the patient.[20] There is no need for surgical treatment for grade 1 and 2 cases, in the absence of secondary disturbances. In more aggressive cases (grade 3) curettage appears to be necessary to reduce the maxillofacial deformity that occurs after puberty. Waiting for disease regression, followed by the evaluation of physiologic bone remodeling, is the most commonly recommended treatment approach.[31] In the present cases, we preferred to wait for spontaneous regression of lesions, and the outcome was excellent in cases 1 and 2, with significant regression of lesions. According to Dukart et al., surgical curettage and recontouring performed during a period of rapid growth of cherubism lesions not only offer a favorable immediate result but also arrest active growth of remnant lesions while stimulating bone regeneration.[32] However, prompt recurrence is likely to happen when surgery is performed at an early stage because it has been observed that lesions do not progress after puberty and the jaws tend to acquire the normal configuration at adulthood.[20] Son et al.[33] presented the first case of innovative surgery for cherubism, consisting of recontouring of the orbital floors with resorbable plates and infracturing of the mandible by using sagittal split osteotomies. Calcitonin therapy may be effective and has resulted in remission of lesions, probably by inhibiting osteoclastic activity of the giant cells and preventing further involvement of jaws.[34] Radiation therapy is ineffective and is contraindicated

because there is the risk of osteoradionecrosis or even malignant transformation resulting in osteosarcoma. Radiation therapy can also interfere with dentofacial growth and development and adversely affect the results of future surgical procedures.[31] Recently, the tumor necrosis factor-α antagonist adalimumab was tried in 2 patients, but it did not result in sufficient improvement.[35]

The mother of the patient in case 1 presented with a very unusual finding of secondary giant cell palatal lesion, which had developed in the later phase of life after remodeling of the jaws affected by cherubism lesions in childhood. No such case has been reported in the literature. Some studies stated that no mutation was found in the *SH3BP2* gene in central giant cell granuloma and concluded that cherubism is a separate entity and that somatic mutation in a specific group of cells can cause focal lesions in giant cell granuloma.[36,37] However, Argyris et al.[38] described a family with cherubism in which 2 of its members had odontogenic tumors in association with persistent central giant cell lesions. Our case demonstrated a positive history of childhood cherubism, with the lesion eventually involuting after puberty but a secondary giant cell lesion involving palate developing in the fourth decade. Hence, it is advisable to keep patients with cherubism on a lifelong follow-up schedule to monitor for development of any secondary lesions even after involution of childhood cherubism lesions.

CONCLUSIONS

Although cherubism is self-limiting and regresses spontaneously after puberty, patients should be kept under long-term periodic follow-up to closely observe the behavior of lesions and to monitor for the development of any secondary giant cell lesions. Genetic screening should be undertaken to rule out familial involvement, and appropriate genetic counseling should be provided. Surgical intervention should be delayed until the end of puberty. Moreover, surgical treatment is preferred only in cases where lesions are aggressive, causing significant facial deformity and functional impairments. Clinicians should have thorough knowledge of the behavior, management, and prognosis of this disorder.

REFERENCES

1. Ali I K, Karjodkar FR, Sansare K, et al. Non-familial cherubism with bilateral maxilla and mandible involvement—clinicoradiographic findings. *Cureus*. 2016;8:E709.
2. Elshafey R. Imaging of cherubism: case report and review of the literature. *Tanta Med J*. 2014;42:42-45.
3. Deshmukh R, Joshi S, Deo PN. Nonfamilial cherubism: a case report and review of literature. *J Oral Maxillofac Pathol*. 2017;21:181.
4. Wright JM, Vered M. Update from the 4th edition of the World Health Organization Classification of Head and Neck Tumours: Odontogenic and Maxillofacial Bone Tumors. *Head Neck Pathol*. 2017;11:68-77.
5. Arnott DG. Cherubism—an initial unilateral presentation. *Br J Oral Surg*. 1978;16:38-46.
6. Kalantar Motamedi MH. Treatment of cherubism with locally aggressive behavior presenting in adulthood: report of four cases and a proposed new grading system. *J Oral Maxillofac Surg*. 1998;56:1336-1342.
7. Raposo-Amaral CE, Campos Guidi MD, Warren SM, et al. Two-stage surgical treatment of severe cherubism. *Ann Plast Surg*. 2007;58:645-651.
8. Papadaki ME, Lietman SA, Levine MA, Olsen BR, Kaban LB, Reichenberger EJ. Cherubism: best clinical practice. *Orphanet J Rare Dis*. 2012;7:S6.
9. Degala S, Mahesh KP, Monalisha. Cherubism: a case report. *J Maxillofac Oral Surg*. 2015;14:258-262.
10. Baskin B, Bowdin S, Ray PN, et al. Cherubism. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJ, eds. *Gene Reviews*, Seattle, WA: University of Washington Seattle; 1993.
11. Etoz OA, Dolanmaz D, Gunhan O. Treatment of cherubism with salmon calcitonin: a case report. *Eur J Dent*. 2011;5:486-491.
12. Redfors M, Jensen JL, Storhaug K, Prescott T, Larheim TA. Cherubism: panoramic and CT features in adults. *Dentomaxillofac Radiol*. 2013;42:20130034.
13. Silva EC, Silva GCC, Vieira TC. Cherubism: clinicoradiographic features, treatment, and long-term follow-up of 8 cases. *J Maxillofac Oral Surg*. 2007;65:517-522.
14. Singh A, Singh K, Goel R, Hu Y, Reichenberger, Kapoor S. Genetic study of an Indian family with cherubism. *Indian J Pediatr*. 2014;81:299-301.
15. Chuong R, Kaban LB, Kozakewich H, Perez-Atayde A. Central giant cell lesions of the jaws: a clinicopathologic study. *J Oral Maxillofac Surg*. 1986;44:708-713.
16. Kaur M, Shah S, Babaji P, Singh J, Nair D, Kamble SS. Cherubism: a rare case report. *J Nat Sci Biol Med*. 2014;5:488-491.
17. Ueki Y, Lin CY, Senoo M, et al. Increased myeloid cell responses to M-CSF and RANKL cause bone loss and inflammation in SH3BP2 "cherubism" mice. *Cell*. 2007;128:71-83.
18. Kadlub N, Sessiecq Q, Mandavit M, et al. Molecular and cellular characterizations of human cherubism: disease aggressiveness depends on osteoclast differentiation. *Orphanet J Rare Dis*. 2018;13:166.
19. Holley TJ, Giannini PJ, Narayana N, Desa VP. Early detection of "cherubism" with eventual bilateral progression: a literature review and case report. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;127:e77-e83.
20. Gomes MF, De Souza Setubal Destro MF, De Freitas Banzi EC, Dos Santos SH, Claro FA, Oliveira Nogueira TD. Aggressive behaviour of cherubism in a teenager: 4-years of clinical follow up associated with radiographic and histological features. *Dentomaxillofac Radiol*. 2005;34:313-318.
21. Trivedi A, Gupta SD, Sharma S, Mehta R. Nonfamilial cherubism. *J Indian Soc Pedod Prev Dent*. 2013;31:43-47.
22. Brix M, Peters H, Lebeau J. Cherubism. *Rev Stomatol Chir Maxillofac*. 2009;110:293-298.
23. Ducours JL, Ducours M. Cherubism: a case followed for 18 years. *Ann Chir Plast Esthet*. 2013;58:152-158.
24. Thompson N. Cherubism: familial fibrous dysplasia of the jaws. *Br J Plast Surg*. 1959;12:89-103.
25. McClendon JL, Anderson DE, Cornelius EA. Cherubism—hereditary fibrous dysplasia of the jaws: II. Pathologic considerations. *Oral Surg Oral Med Oral Pathol*. 1962;15:17-38.

26. Wayman JB. Cherubism: a report of three cases. *Br J Oral Surg*. 1978;16:47-56.
27. Timoşca GC, Găleşanu RM, Cotuţiu C, Grigoraş M. Aggressive form of cherubism: report of a case. *J Oral Maxillofac Surg*. 2000;58:336-344.
28. Colombo F, Cursiefen C, Neukam FW, Holbach LM. Orbital involvement in cherubism. *Ophthalmology*. 2001;108:1884-1888.
29. Font RL, Blanco G, Soparkar CN, Patrinely JR, Ostrowski ML. Giant cell reparative granuloma of the orbit associated with cherubism. *Ophthalmology*. 2003;110:1846-1849.
30. Battaglia A, Merati A, Magit A. Cherubism and upper airway obstruction. *Otolaryngol Head Neck Surg*. 2000;122:573-574.
31. Lima G, de MG, Almeida JD, Cabral LAG. Cherubism: clinicoradiographic features and treatment. *J Oral Maxillofac Res*. 2010;1:e2.
32. Dukart RC, Kolodny SC, Polte HW, Hooker SP. Cherubism: report of case. *J Oral Surg*. 1974;32:782-785.
33. Son JH, Marshall DC, Valiathan M, et al. Innovative surgical treatment of severe cherubism. *Cleft Palate Craniofac J*. 2019;56:90-93.
34. de Lange J, van den Akker HP, Scholtemeijer M. Cherubism treated with calcitonin: report of a case. *J Oral Maxillofac Surg*. 2007;65:1665-1667.
35. Hero M, Suomalainen A, Hagström J, et al. Anti-tumor necrosis factor treatment in cherubism—clinical, radiological and histological findings in two children. *Bone*. 2013;52:347-353.
36. Teixeira RC, Horz HP, Damante JH, et al. SH3BP2-encoding exons involved in cherubism are not associated with central giant cell granuloma. *Int J Oral Maxillofac Surg*. 2011;40:851-855.
37. de Lange J, van Maarle MC, van den Akker HP, Redeker EJ. DNA analysis of the SH3BP2 gene in patients with aggressive central giant cell granuloma. *Br J Oral Maxillofac Surg*. 2007;45:499-500.
38. Argyris PP, Gopalakrishnan R, Hu Y, Reichenberger EJ, Koutlas IG. Clinicopathologic and molecular characteristics of familial cherubism with associated odontogenic tumorous proliferations. *Head Neck Pathol*. 2018;12:136-144.

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