

CASE REPORT

Aggressive behaviour of cherubism in a teenager: 4-years of clinical follow-up associated with radiographic and histological features

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Cherubism is a rare hereditary fibro-osseous childhood disease characterized by bone degradation and fibrous tissue replacement at the angles of the mandible and at the tuberosity areas of the maxilla that leads to prominence of the lower face and an appearance reminiscent of the cherub's portrayal in Renaissance art. This disease has an autosomal dominant hereditary characteristic. The purpose of this report is to analyse laboratory tests, clinicopathological and radiographic features of cherubism and its intraoral manifestations in a patient during 4-years of follow-up, correlating the features observed in this case with those of the literature. Also discussed is the atypical and aggressive behaviour of this case during puberty.

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Case report

A 13-year-old female leucoderm patient was referred to Bioscience Center for Special Health Care Needs at São José dos Campos Dental School, São Paulo State University (UNESP) presenting painless swelling of the cheeks with discrete facial asymmetry, showing the right side more developed than the left with bilateral lymphadenopathy in the submandibular region (Figure 1).

No known cases of cherubism involving her biological father, mother, two younger brothers or other relatives were found during the review of the patient's family medical history. The menarche of this female patient occurred when she was 11 years old.

At extraoral evaluation, the expression and colour of the face were normal and the eyes did not reveal any abnormalities. At intraoral clinical examination, the

absence of the lower right first and second molars and the lower left second molar with bilateral eversion of the vestibule were observed. The mucosa of the right side showed a rigid consistency, whiteness and marks made by the occlusal surfaces of antagonist teeth, but the left side displayed a normal aspect.

For radiological study, lateral and panoramic radiographs and computed tomography (CT) were obtained. The images showed bilateral multilocular lesions located in the body, angle, ramus and coronoid process of mandible, not affecting the condyles. In the right side, with the absence of the lower first molar, the second molar was found dislocated to the base of the mandibular bone and the third molar was directed towards the lingual cortex and mandibular angle. Their roots were incompletely formed. In the left side, the lower second molar was located below the first molar, which presented severe resorption of the distal root. The lower third molar was floating within the lesion. The maxilla showed absence of the disease and absence of the first left and right molars (Figure 2). The lateral radiographic view showed displaced lower posterior

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Figure 1 Facial appearance of reported case showing swelling of the cheeks with discrete facial asymmetry of the right side

teeth at the lesion in both the anteroposterior and inferosuperior direction. The cortical bone was expanded but not disrupted, although it was very thin. On the coronal CT scan the lesion showed a hypoattenuated heterogeneous image with precise and irregular limits extending from the anterior to the posterior direction of the mandible. The image of the lesion observed in the right side showed larger volume than in the left side (Figure 3).

The results of the laboratory tests were within normal limits for alkaline phosphatase (33 IU l^{-1} ; normal: adults $13\text{--}43 \text{ IU l}^{-1}$, child $56\text{--}156 \text{ IU l}^{-1}$), calcium (9.3 mg dl^{-1} ; normal: $8.8\text{--}11.0 \text{ mg dl}^{-1}$), phosphorus (3.8 mg dl^{-1} ;

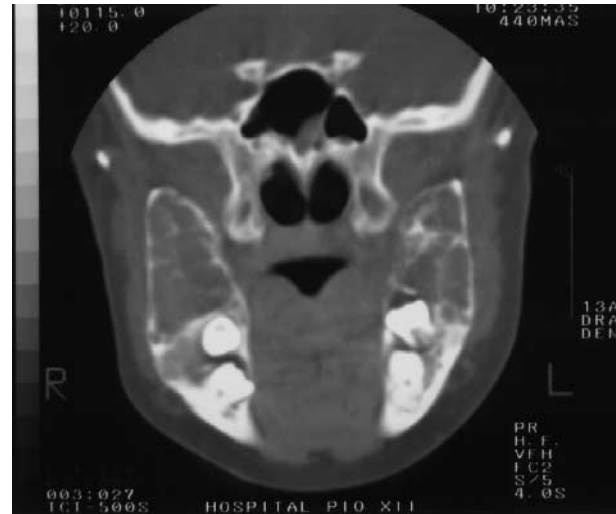


Figure 3 The coronal CT scan revealing hypoattenuated heterogeneous image with precise and irregular limits extending from the anterior to the posterior direction of the mandible

normal: adult $2.5\text{--}4.8 \text{ mg dl}^{-1}$, child $3\text{--}7 \text{ mg dl}^{-1}$), and parathyroid hormone levels (15 pg ml^{-1} ; normal: $13\text{--}54 \text{ pg ml}^{-1}$).

An incisional biopsy in the left mandibular area of the lesion was performed and histological sections showed a mass of loose connective tissue containing a few small multinucleated giant cells, discrete number of blood vessels, focus of red blood cells haemorrhage and various mature bone trabeculae (Figure 4). The clinical, radiographic, laboratory and microscopic features of the lesion suggested a diagnosis of cherubism. The differential diagnosis could be central giant cell granuloma, but this lesion occurs generally anterior to lower first molars and in general is more vascularized and has more interstitial haemorrhage and its superficial colour is red-bluish.

After 4 years of follow-up, the patient still showed bilateral enlargement of the face with asymmetry (Figure 5). On intraoral examination, it was noted that the opening of the mouth was limited to approximately 2.0 cm. The lower posterior teeth were tilted in a lingual direction.



Figure 2 Panoramic radiograph showing bilateral multilocular lesion located in the body, angle, ramus, and coronoid process of mandible, not affecting the condyles, and displacement of the right lower second molar to the base of the mandibular body and the third molar to the cortical lingual and mandibular angle; their roots presented incomplete formation; in the left side, the lower second molar was located below the first molar that presented severe resorption of the distal root; the lower third molar was floating within the lesion

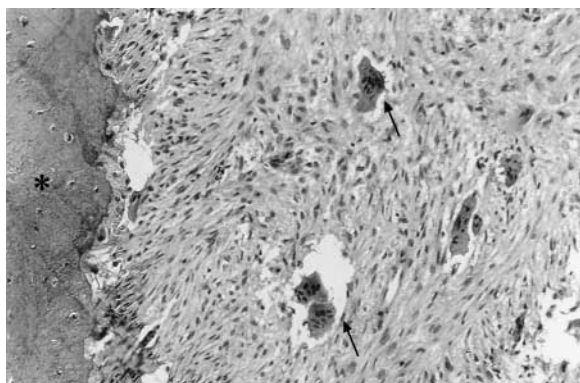


Figure 4 Photomicrography revealing smooth connective tissue with multinucleated giant cells (arrows), focus of red blood cells extravasation and mature bone trabeculae (asterisk) (haematoxylin and eosin, original magnification, 200 ×)

The temporomandibular joints did not exhibit clinical alterations. The bilateral eversion of the vestibule was shallower compared with the first examination done in the patient. The total eruption of the right lower third molar, the partial eruption of the left lower third molar, and total eruption of the upper left and right third molars were observed. The oral mucosa at these regions showed normal aspects.

Radiological findings from lateral and panoramic radiographs showed expansion of the lesion with multi-locular features at the coronoid process, ascending ramus, mandibular angle and anterior region of the mandible, but not affecting the condyles. There were no signs of the



Figure 5 Extraoral view, after 4-years clinical follow up, showing bilateral enlargement of the face with permanence of the facial asymmetry at the right side

lesion in the maxilla. The lower second molars remained surrounded by lesion (Figure 6). The axial CT scan revealed the expansion of the lesion with poor thickness of the cortical bone at the angle and ramus of the mandible (Figure 7). In the 3D reconstruction of the CT scan at front and lateral views, the bilateral vestibular and lingual cortical bones of the retromolar region were thin and/or eroded, exhibiting multiple deeper depressions more in the right than in the left side. There was absence of the lesion in the condylar processes and the cortical bone of the mandibular basis showed normal features (Figure 8).

The results of the laboratory tests remained within normal limits for alkaline phosphatase (20 IU l^{-1}), calcium (8.6 mg dl^{-1}), phosphorus (4.1 mg dl^{-1}), and parathormone levels (21.30 pg ml^{-1}).

During surgical procedure of the second incisional biopsy, accomplished in the left and right mandibular angle, it was observed that the cortical bone showed areas of erosion and perforation once the lesion was exposed. The lesion showed soft consistency and no adherence to bone walls. The histological characteristics revealed loose connective tissue and few multinucleated giant cells when compared with the aspects of the first biopsy. Discrete number of blood vessels, various mature bone trabeculae and osteoid tissue were also shown (Figure 9). The clinical, radiographic, laboratory and microscopic features of the lesion confirmed the diagnosis of cherubism.

Discussion

The patient reported here exhibited an asymmetric expansion of the mandible and did not relate any pain from the disease. Considering the size and extent of the lesions and the clinical aspect of the patient, cherubism was diagnosed. Reports of cherubism in the literature range from minor lesions without hard tissue destruction and facial deformity to destructive lesions with massive involvement of the maxilla as well as the mandible.^{1–3}

Cherubism usually is diagnosed early in childhood, often in the first decade of life. Classically, the affected child is normal at birth and develops the disease in the second or third year of life. The mean age for the development of clinical aspects of the disease is 7 years and it tends to become more evident until puberty after which spontaneous involution may occur,^{4–7} which did not happen in our case.

The pathogenesis of cherubism remains controversial. No cause and effect relationship with trauma, infection or haemorrhage has ever been verified.⁸ Most cases of cherubism are familial and inherited in an autosomal dominant pattern with high penetrance.^{9,10} According to the evaluation of the patient's clinical history, no case of cherubism was observed spanning four generations. Researchers have described seven mutations in the gene encoding SH3-binding protein SH3BP2 on chromosome 4p16.3 that cause cherubism.^{9,10} The penetrance is approximately 80% (100% in males, 50% to 70% in females), although the precise estimation will depend on



Figure 6 Panoramic radiograph showing bilateral growth of the lesion in the body, ramus, and coronoid process of mandible; atypical eruption of the right lower third molar; and resorption of the distal root of the left lower first molar

whether clinical or radiological diagnostic criteria have been used.^{4,8,11}

Cherubism has been associated with other genetic disorders, including a number of cases of both Noonan-like syndrome (short stature, low-normal intelligence, ocular hypertelorism, prominent posterior angulated ears, giant-cell lesions of the bones, joints, and soft tissue, *pectus excavatum*, and pulmonary stenosis) and Ramon syndrome (short stature, mental retardation, epilepsy, gingival fibromatosis and hypertrichosis), but the incidence for this connection with other diseases requires more investigations.^{11–13}

Clinically, cherubism is characterized by swelling of the cheeks and jaws, is painless, firm and hard to palpation, the colour of the face is normal, it is often symmetrical, resulting in a round face, sometimes with retrusion of the lower eyelids, and exposure of the sclera below the pupil producing the characteristic cherubic appearance, like in Renaissance portrayals of angels.^{4,9,14} The most aggressive lesions may affect deglutition, swallowing, breathing and speech,¹⁵ but that was not observed in the present case report. According to Katz and Underhill,⁴ this pathological

entity may also develop adenopathy in the most developed stage.

Intraoral evaluation of cherubism shows bone expansion that is firm and hard to palpation, with intact overlying mucosa.^{13,14} In addition to premature exfoliation of deciduous and permanent teeth in the involved areas, agenesis, malformation, ectopic and unerupted teeth could also occur.^{4,9} In the present case, we verified alterations of the posterior teeth in both sides of the mandible. Root dilaceration in tooth 47 probably happened owing to its compression and displacement against cortical bone, which is a well known resistant bone zone. We believe that the left first molar distal root was resorbed due to severe displacement of the second molar caused by growing of the lesion. The recommended attitude to avoid an increased radicular resorption is the endodontic treatment of the roots involved in the lesion process.

Early third molar eruption could explain the slower growth of the lesion after puberty when compared with the rapid growth between 13 years and 16 years of age. The slowing of this growth could be a result of the increase of sex hormones rates in the teenagers. The hormones act directly in the inhibition of osteoclastogenesis and/or osteoclasts functions.³

Radiographic appearances of cherubism have been described as unilocular or multilocular, bilateral radiolucent lesions with ragged, poorly defined borders, located in the mandible,^{2,4,9,16} similar to our findings. Furthermore, it was verified that the cortical bone at the mandibular base was thin but not disrupted even though there was expansion of the bone, indicating the benign behaviour of cherubism. Another factor that could sustain the benignity of the lesion would be the integrity of the mandibular nerve. Based on observations by Faircloth and colleagues,⁸ the lesion may affect the coronoid process but not the condyle, which was also observed in our case. Probably, expansion did not occur at the condyle region because it exhibits a great quantity of compact bone with few bone marrow spaces, causing difficulties to the invasion by cherubism. However, there are some cases which present bilateral involvement and have affected the condyle as described by Reade *et al.*¹⁷

Depending on the aggressive clinical course of the disease, some authors relate that cortical bone perforation

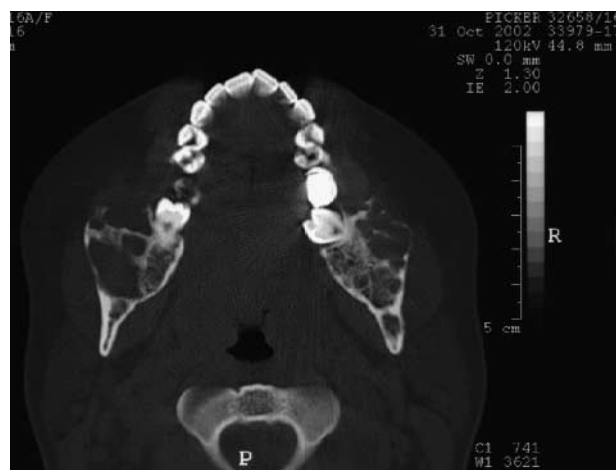


Figure 7 Axial CT scan showing the expansion of the lesion and thinness of the cortical bone at the angle and ramus of the mandible

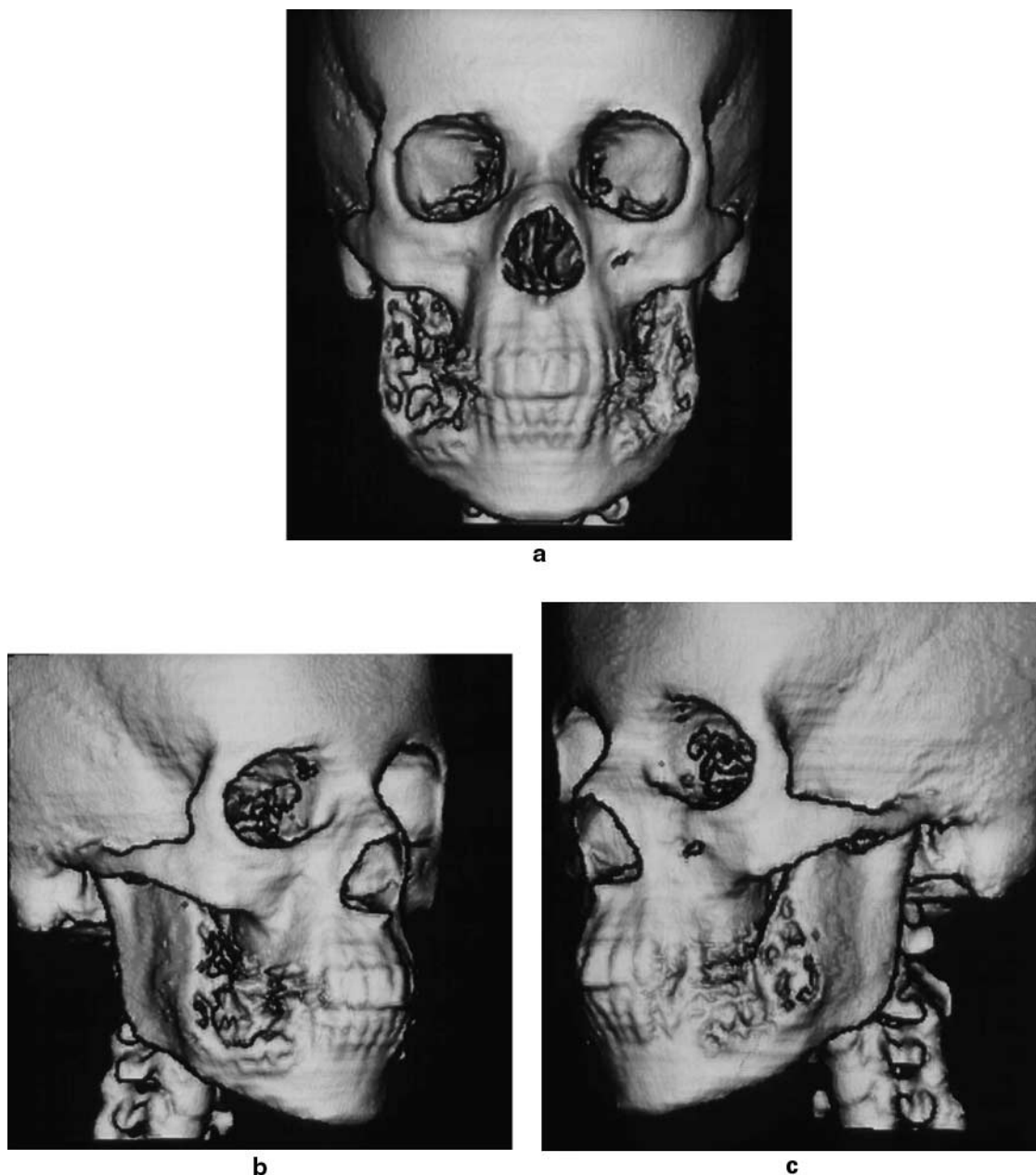


Figure 8 (a,b,c) 3D reconstruction of the CT scan images (coronal and sagittal views) showing erosive aspect and multiple depressions at the bilateral vestibular cortical bone of the retromolar region

may occur and the area becomes susceptible to fractures and/or infections.^{4,8} In our case the normal mandibular bone at the angle was substituted by multiple radiolucent areas bilaterally, well-defined and separated by osteoid septae. In the CT scan axial view of the cranium, the lesion extended from the anteroposterior direction and presented itself larger in the right side than in the left side.

Cherubism does not involve other bones of the skeleton or general bone metabolism.¹⁸ The biochemical bone markers, such as serum calcium, phosphorus and alkaline phosphatase, have been found within the normal ranges for the respective age.^{9,19,20} This was also so in our case.

Histopathological evaluation of the lesions showed proliferating loose connective tissue containing few multinucleated giant cells. The stroma contained focal deposits of haemosiderin pigment. Small vessels may show perivascular collagen cuffing. Osteoid and bone tissue formation were often seen at the periphery of the lesion tissue, results that have also been observed by Katz and Underhill,¹⁵ Hitomi *et al*,²² and Mangion *et al*.¹¹ Southgate and coworkers³ established that multinucleated cells in the cherubism are osteoclasts since they synthesized tartrate-resistant acid phosphatase, expressed vitronectin receptors, promoted bone resorption at culture and the multinucleated giant cells were inhibited by calcitonin *in situ*.

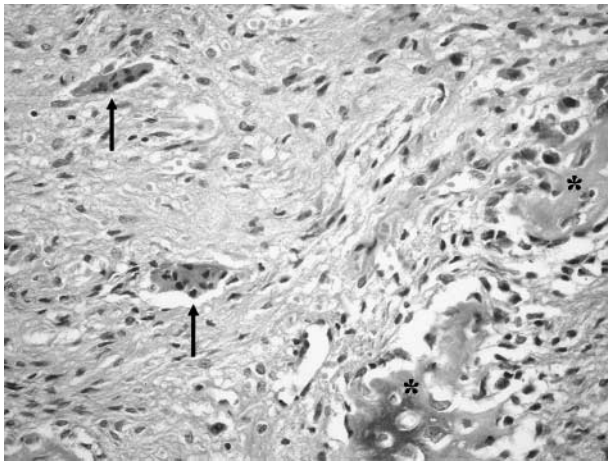


Figure 9 Photomicroscopy showing connective tissue with low cellularity and smaller quantity of the multinucleated giant cells (arrows) when compared with the aspects of the first biopsy; mature bone trabeculae and osteoid tissue (asterisk) were observed (haematoxylin and eosin, original magnification, 400 ×)

Treatment of cherubism has not been standardized, making it difficult to indicate a treatment protocol. The possibility of spontaneous involution is recognized, but the frequency is not known since most of the patients have been treated surgically prior to adulthood.⁸ Often, the disease involutes spontaneously when children reach puberty. The reason why this occurs is not clear, but osteoclast formation is reduced by sex steroid hormones, and plasma concentrations of oestrogen and testosterone increase at puberty. It has been suggested that a genetic defect is responsible for the localized increase of

osteoclasts in cherubism because of the physiological increased synthesis of sex steroid hormones.⁸ The indication for treatment of cherubism is based on the rate of the lesion's progression, the extent of its involvement and the emotional state of the patient.

Therefore, many investigators recommend to delay treatment until after puberty unless psychological problems occur at an earlier age.^{8,21} Prompt recurrence is likely when surgery is performed at an early age. It is noted that cherubism does not progress after puberty and as the patient grows to adulthood, the entire jawbone lesion tends to show a more normal configuration. Sufficient removal of tissue by enucleation or curettage of the tumoural tissue appears to be useful in more aggressive cases as this one present here, in order to reduce maxillofacial deformity.^{7,8,22} Radiation therapy is ineffective and contraindicated considering the risks of osteoradionecrosis, and interference with dental facial growth and development.^{7,8}

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