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CASE STUDY

Cherubism with peripheral reparative giant cell granuloma in the mandible and maxilla

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ABSTRACT

Cherubism is an autosomal dominant disease that causes abnormal osteoblast-osteoclast function, resulting in progressive enlargement around the maxillofacial area due to replacement of normal bone with fibrous tissue and immature bone. The clinical and radiographic signs of cherubism include bilateral radiolucent multi-ocular lesions of the mandible and maxilla, causing bilateral cheek swelling. A 9-year-old boy came to the Oral Surgery of Sardjito Hospital, Yogyakarta, with a complaint of enlargement of both cheeks nine months ago. The patient complained that the swelling on the maxilla enlarged and felt disturbing for his appearance. The enlargement was painless, not easy to bleed, hard, and disturbing when eating and sleeping. Radiograph examination demonstrated bilateral maxillary and mandibular multi-ocular-radiolucent lesions. Three stages of surgery were performed: biopsy-incision with the histopathological result being benign fibrous histiocytoma, curettage-reshaping of the mandible 1 month after biopsy, and curettage-reshaping of the maxilla 9 months after the mandible surgery. The histopathological test of the lesions in the maxilla and mandible showed the same result: peripheral reparative giant cell granuloma. Twelve months postoperatively, the patient had no complaints, showed no disturbances in eating and sleeping, and regained a symmetrical face. The patient's initial curettage and reshaping resolved the masticatory complaints, improved facial aesthetics, and reduced lesions' expansion at the bilateral mandibular and maxillary bones.

Keywords: cherubism; giant cell; granuloma; osteoclast; reparative

INTRODUCTION

Cherubism is a rare, non-neoplastic, and self-limiting hereditary progressive fibro-osseous lesion involving both maxillary and mandibular bones.[1] The fibro-osseous lesion arises as a result of abnormal function of osteoblasts and osteoclasts, leading to the replacement of normal bone by fibrous tissue and immature bone. The characteristic of cherubism is localized painless bone enlargement in cherubism around the bilateral facial bones.[2] Cherubism is a hereditary and non-hereditary autosomal dominant disease that is inherited in 90-100% male and 50-70% female.[3] According to Bhattacharya and Mishra, the penetration of gene expression in this autosomal dominant lesion is 100% in male, and only 75% occurs in female. This syndrome is more prevalent in the mandibular area. Cherubism is usually detected at the age of 14 months to 5 years.[3] Lesion may disappear on its own during adolescence or up to 30 years of age.[4,5]

Cherubism is a familial autosomal dominant disease mapped to the chromosome 4q16.3.5. The mutation occurs in the SH3BP2 gene, which encodes c-Abl-binding protein. However, some studies suggest that even if there is no mutation found in the gene, it does not rule out the possibility of cherubism. The appearance of cherubism in a histological examination cannot be distinguished from Giant cell granuloma with a picture of fibrous tissue, giant cell osteoclast re-formation, and additional stromal fibrosis and hemosiderin.[3]

The classification of cherubism differentiates the type of lesion from the involvement of root

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resorption, the aggressiveness degree of tissue expansion, to the area involved in the mandible and maxilla. Clinical and radiologic features of cherubism include radiolucent, symmetrical, multilocular, expansive lesions of the maxilla and mandible, appearing at 2-7 years old.[5] The enlargement of the submandibular lymph nodules in the early stages due to dysplastic fibrous soft tissue expansion may infiltrate the orbital floor, cause lifting of the eyes, and expose the sclera under the eyes. Cherubism lesions are limited to the jawbone and, in most cases, will develop by adolescence.[6] Informed and written consent was obtained for the case, treatment, and publishing of photographs from the patient's parents. The patient's parents agreed to publish the case and photographs.

METHODS

A 9-year-old male patient came to the Oral and Maxillofacial Surgery Department of Sardjito Hospital, Yogyakarta with complaints of enlargement of the right and left cheeks. The enlargement appeared 9 months before the first visit, without any pain and bleeding with hard texture. History of allergy and systemic disease was denied. The extraoral examination revealed asymmetrical face with swelling on the right (sized 3x2×1.5 cm) and left cheek (sized 2x2x1.5 cm) without any pain, and the color was the same as the surrounding tissue with a normal temperature. There were no paresthesia and infraorbital area pressure. There were no signs of lymphadenopathy. The intraoral examination revealed lumps on the upper and lower jaw on the right and left sides, with hard consistency, no ping pong effect observed, no pain and not bleeding-prone, and color and temperature being the same with the surrounding tissue. The patient's Multislice Computerized Tomography (MSCT) image showed expansive hypodense lesions on the maxilla and mandibular ramus bilaterally, accompanied by thinning of the cortex and dental images inside the lesion and septa formed. The patient's parental history revealed that the patient's father and grandmother had also experienced similar lesions when they were in their teens but had undergone surgery. At that time, the patient's father and grandmother were diagnosed with Giant Cell Granuloma. Three months before, a biopsy surgery was performed along with IHC examination with the results of Benign histiocytoma (IHC), and the differential diagnosis was Giant Cell Granuloma (biopsy). The patient was referred to the endocrine and genetics department and diagnosed with cherubism et causa Goldenhar Syndrome. Then, the patient was curetted, and the tumor on the bilateral mandible was reshaped using General Anesthesia (GA). The results of the lesion were taken and sent to the Anatomical Pathology department of Sardjito Hospital. The results were capsule-less connective tissue with many foreign body type giant cells, fibrous stroma with dilatation and proliferation of blood vessels, bleeding area with enough lymphocytes, and neutrophils and epithelioid histiocytes leading to peripheral reparative giant cell granuloma. The patient felt that the complaints had decreased, and the face felt symmetrical.

The patient came 11 months later complaining of the same problem in the upper jaw. The Multislice

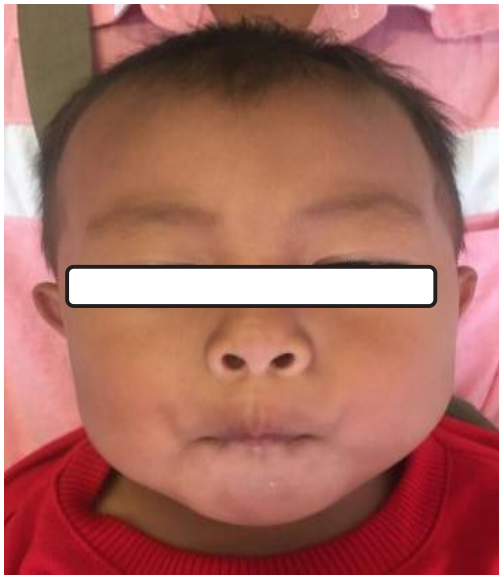

Figure 1. Patient's extraoral photograph before surgery

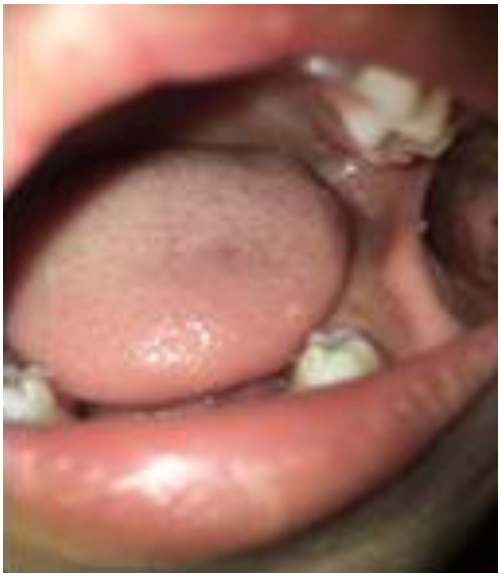

Figure2. Intraoral image before surgery

Figure 3. 3D CT before surgery

Computerized Tomography (MSCT) examination revealed masses in the right angulus, ramus to corpus mandibular and angulus, ramus to part of corpus mandibular sinistra, bilateral maxillae with destruction of posterior aspect maxillary wall and anterior medial aspect mandibular wall, filling maxillary sinus and urging posterior aspect maxillary sinus wall, cerebri oedema, and sinistra maxillary sinusitis. The second operation included curettage and reshaping of the bilateral maxilla that was performed under General Anesthesia after the patient's general condition was qualified to reduce the swelling of the maxilla. The anatomical pathology examination of the lesions revealed fibrotic connective tissue with proliferation of medium to large-sized mononuclear cells with scanty to moderate cytoplasm. Round, oval, spindle, fine chromatin and nucleolus were seen. Many multinucleated giant cells (osteoclast type) and woven bone were observed. In the stroma, vascular proliferation, erythrocyte extravasation, and lymphohistiocytic scattering were found,

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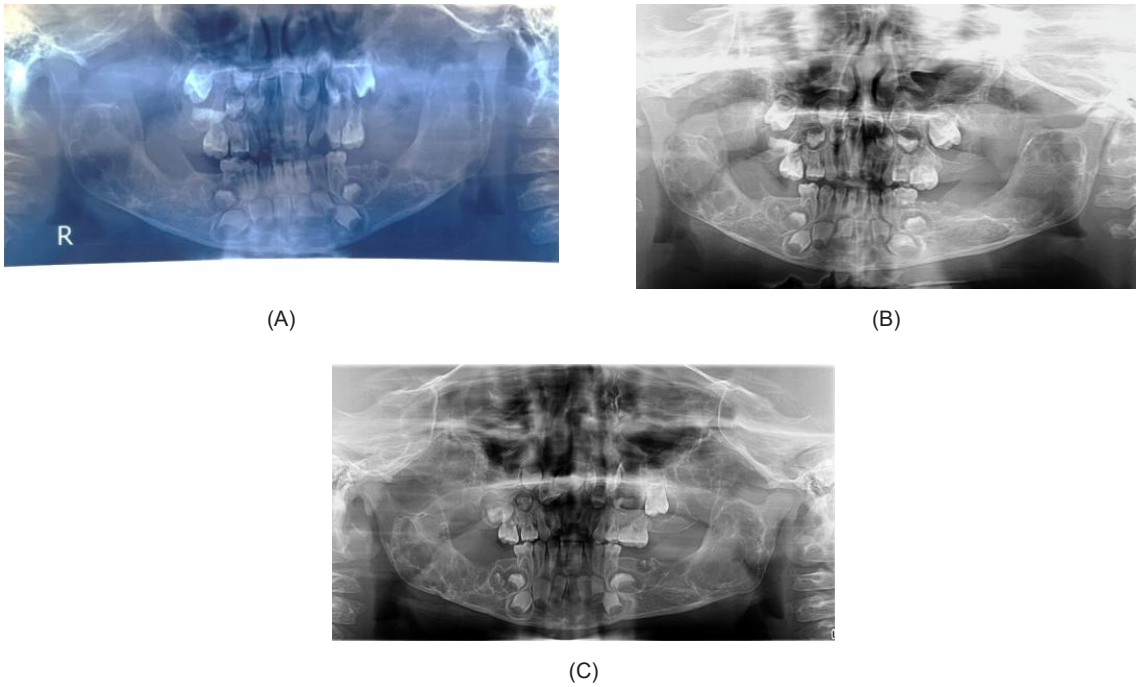


Figure 4. Panoramic Image (A) Before Surgery, (B) After Mandible Reshaping, (C) After Maxilla Reshaping

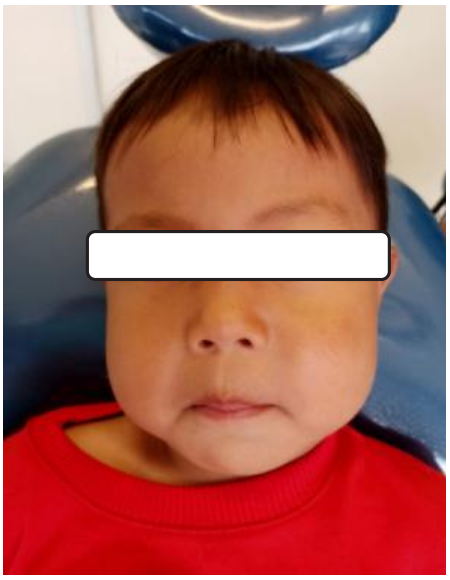


Figure 5. 11 months post curettage and *reshaping*

suggesting recurrent peripheral reparative giant cell granuloma.

Figure 8 (A) shows capsule-less connective tissue with many foreign body-type giant cells. Fibrous stroma with dilatation and proliferation of blood vessels as well as areas of hemorrhage are moderately dotted with lymphocytes, neutrophils, and epithelioid histiocytes. Meanwhile, Figure 8 (B) shows fibrous connective tissue with proliferation of medium to large-sized mononuclear cells with scanty to moderate cytoplasm. Round, oval, spindle, fine chromatin, and nucleolus are seen. Many multinucleated giant cells (osteoclast type) and woven bone are observed. Both the

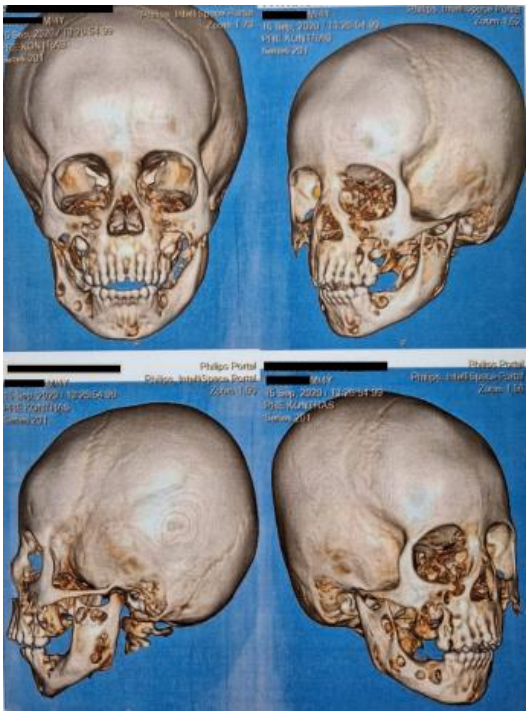


Figure 6. 3D CT 11 months post curettage and mandible *reshaping*

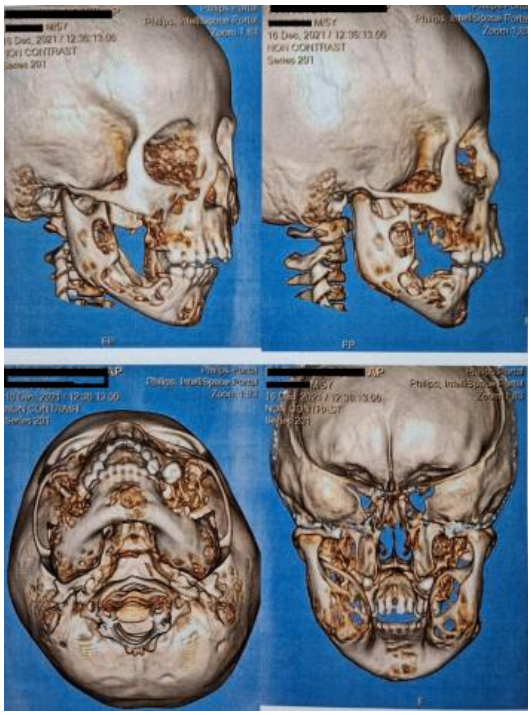
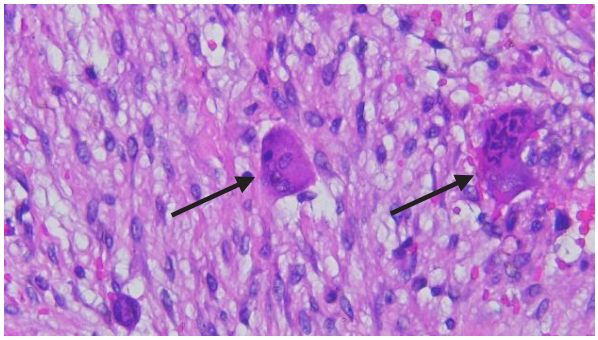
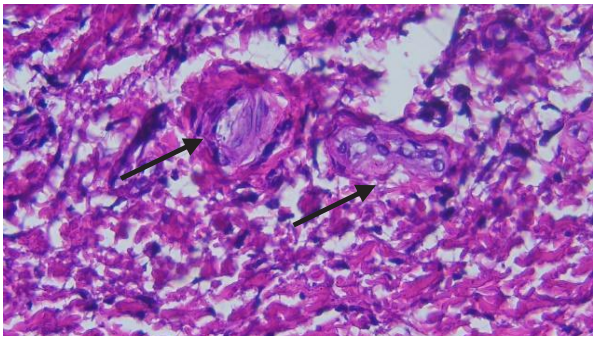


Figure 7. 3D CT 11 months post curettage and mandible *reshaping*



(A)



(B)

Figure 8. Microscopic images of mandibular (A), and maxillary (B) biopsy tissues, depict multinucleated giant cells (arrows) in the fibroblastic stromal area (Stained with Hematoxylin and Eosin at 200x magnification)

anatomical pathology examinations showed the same characteristic of multinucleated giant cells, as indicated by the arrow.

DISCUSSION

The patient's lesion was detected at the age of 4 years. This is in accordance with Papadaki et al, who states that lesion is usually detected at the age of 2-7 years when the swelling starts, with symmetrical development of multilocular radiolucent and widespread pattern in the lower and/or upper jaw, which usually appears first.[7,8] The submandibular and neck lymph nodes will experience swelling in the early phase. The first radiographic sign of cherubism is usually found in the angular region of the mandible. These radiolucent lesions are usually asymptomatic but may affect the development or eruption of permanent molars, usually in the form of multiple

symmetrical lesions in the mandible and/or maxilla with single or multilocular lesions.[9] The possible differential diagnosis in these cases include Giant Cell Fibroma, Giant cell granuloma, hyperparathyroidism, fibrous dysplasia, and multiple odontogenic keratocysts. These diagnoses can be eliminated because the bilateral pattern of the lesion is off-center. The suspect of hyperthyroidism did not need to be tracked as there were no clinical signs.[10]

Cherubism is an autosomal dominant disease with more prevalence in male, the gender of our patient. In our case, the gene mutation examination was not carried out, but cherubism was concluded from the results of clinical, radiographic, and anatomical pathology examinations.[6] The histopathological examination of the maxilla and mandible showed relatively the same results, namely fibrous connective tissue with proliferation of medium to large mononuclear cells with little to moderate cytoplasm. Round, oval nuclei, spindle, fine chromatin, and nucleolus were seen. Many multinucleated giant cells (osteoclast type) and woven bone were observed. Blood vessel proliferation, erythrocyte extravasation, and lymphohistiocytic scattering were found in the stroma, leading to recurrent peripheral reparative giant cell granuloma. These results are in accordance with the histopathological picture in cherubism where the lesions in the syndrome cannot be separated from the picture of giant cell granuloma lesions, the general description of which was mentioned by Elshafey in 2014 in the form of fibrous tissue proliferation lesions containing multinucleated giant cells. These cells are foreign bodies with 5-20 nuclei. In some cases, the formation of new bony protrusions between the fibrous tissue can be seen.[9]

Swelling of the mandible was detected in 2019 when the child was 9 years old. After curettage and reshaping, the lesion reappeared in 2020 in the maxilla. This is consistent with the diagnosis of Cherubism which is limited to the jaw bone only. According to the classification summarized by Papadaki et al in 2012, this case is included in Grade 2 class 2 where the lesion involves the mandible and maxilla without signs of root resorption and extends to the anterior area of the maxilla. Swelling in patients with this disease can cause bone resorption, protrusion of the bony cortex area, deformity of the facial bones, compression of the nerve area, nasal obstruction, and backward positioning of the tongue.[11]

Cherubism has a good prognosis, with treatment revolving around aesthetic improvement, chewing function, biopsy, and curettage. This is similar to some literature, which states that the lesion is benign and can decrease and improve when the patient becomes an adolescent.[12,13] Cherubism treatment can include radical surgery, curettage, reshaping, or reconstruction. Surgery is sometimes performed in 2 periods to reduce the amount of blood loss during surgery. Treatment with curettage and reshaping is performed at the age of 9 when there are complaints of mastication, aesthetics, and function, i.e., closing the mouth while sleeping. This is consistent with Tekin et al, stating that generally the surgery is performed when the patient and the parents complaint about swallowing disorders, airway obstruction, and tongue pressing in the child until puberty, ranging in age from 5 to 15 years old. Surgery is performed after the patient's parents understand the explanation that the lesion can improve on its own as the patient grows up. The treatment only aims to reduce the patient's symptoms and complaints. Some studies used calcitonin, but the results were not significant. Radiotherapy is not recommended for the treatment of these lesions because the lesions are benign and radiotherapy could inhibit jaw growth, osteonecrosis, and even trigger malignancy.[14,15] Follow-up treatments such as prostheses and orthodontics are needed to improve the patient's masticatory function.[16]

The patient's complaints about the swelling in the cheek area have decreased 9 months after surgery, the face looks symmetrical, complaints about mastication are gone, the patient can chew well, and there are no complaints of open mouth when sleeping. The Multislice Computerized Tomography (MSCT) results showed that there were still residual lesions in the mandibular ramus

area. Still, it was decided to be observed as the patient develops and grows because lesions in cherubism are a self-limiting disease.[2] Fibro-osseous lesion of cherubism in some studies are detected in childhood, develop at puberty, improve during adulthood, and are even found until the patient is 30 years old if detection is late.[1]

CONCLUSION

Cherubism generally causes bilateral swelling of the mandible and/or maxilla without any pain but may interfere with the patient's respiratory, chewing, and aesthetic functions. Surgical procedures such as resection, curettage, reshaping, and reconstruction are necessary if the lesions have interfered with these functions and have high aggressiveness. The surgeon needs to consider the potential replacement teeth as well as the direction of lesion expansion in planning surgical treatment. Long-term observation is required in the treatment of this case as this lesion is a benign tumor whose process will stop on its own when entering adolescence or adulthood.

CONFLICT OF INTEREST

The authors declare no competing interests.

INFORMED CONSENT

Informed and written consent was obtained for the case, treatment, and publishing of photographs

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