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Case Report
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# A Rare Case Report of Non-Familial Sporadic Reoccurrence of Cherubism: Difficulties from the Surgeon's Point of View

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## ABSTRACT

*Cherubism is a rare bone dysplasia in children characterized by symmetrical bone resorption limited only to the jaws and diagnosed as bone lesions filled with soft fibrous giant cell-rich tissue that can expand and cause severe facial deformity. Most patients have germline mutations in the gene encoding SH3BP2, a signaling adaptor protein involved in adaptive and innate immune responses. Treatment depends on the clinical course of the disease. The current case report presents a young patient with cysts in frontal region of maxilla without family history, that had recurrences of cysts, and is representing a less documented, rare case. Histological finding at that time was indicating a giant cell granuloma and later a grey tumor. Due to the existence of other pathological findings in the jaws with the presence of giant cells, we had difficulties to diagnose cherubism as surgeons.*

***Key words:*** *cherubism, jaw tumors, mandibular, maxilla, case report*

## Introduction

Cherubism is a rare benign, nonneoplastic bone disease with autosomal dominant genetic condition caused by mutations in SH3-binding protein 2 (SH3BP2) gene with hereditary nature with 80% of familial pattern, but sporadic cases were also reported.[1,2] Disease appears in childhood and is characterized by progressive painless bilateral enlargement of the jawbones and fulness of the cheeks. The disorder typically begins in children between age 2-7 and continues until puberty, in most cases the lesions regress spontaneously. During the growing phase, the jawbone is replaced by a granuloma containing multinucleated giant cells within a fibrous stroma. Cherubism is described as a maxillofacial localized disease only affecting jaw bones, frequently affecting mandibula in 60% of the cases but it can affect maxilla as well. Natural progress of the disease is progression from the age of two to the age of puberty, then stabilizes and turns into subsequent spontaneous regression. Expression range varies from non-symptomatic, indetectable, to aggressive resulting also in lethal cases. In addition to the maxillofacial involvement, respiratory disorders due to obstructive apnea[3] or significant orbital manifestations that may cause proptosis, upward looking of eye's appearance and loss of vision may occur.[4] Standard blood count, serum electrolytes, serum calcium and phosphate concentrations, and TSH, FSH, LH, PTH, PTHrP, T4 and T3 hormones, calcitonin and osteocalcin levels are all within the normal range, but alkaline phosphatase might be increased. However, systemic exploration of cherubism patient is extremely rare and incomplete.[4,5] We investigated potential cherubism in a young patient, but without diagnosis of mutation of an adaptor protein involved in bone remodeling and inflammation. Thus, here we report a sporadic case of cherubism, which was not immediately detected.

## Case Report

An 8-year old female patient presented to our department for the first time in 2003 came with cysts in the frontal region of maxilla. The diagnosis with OPT was confirming multiple cysts in maxillary region. Moreover, ultrasound of the neck showed enlarged lymph nodes in submandibular region in size of 34.2x12 mm. We found unaffected ocular mobility so visual acuity was not as-

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sessed. Family history anamnesis did not involve jaws swellings. Histopathological examination of the tissue was showing giant cell granuloma. Provided with this diagnosis, surgeons justified and performed surgical intervention of cysts removal in maxilla.

After three years, in 2006, the patient returned. CT scan showed dysplastic changes in the lower jaw, recurrent cysts in the upper jaw and palatal bones. A diffuse swelling was noticed in mid-to-lower face region during the extraoral clinical examination (Figure 1). She had clinical characteristics of cherubin face, symmetrical enlargement of the jaws, V arch-shaped palate, loss of teeth, lymphadenopathy and hyperparathyroidism. Laboratory analysis results were: parathormone 77.0 (normal range: 8-74), alkaline phosphate 694.5 (normal range: 100-700). Diagnosis was indicating grey tumor. The patient presented impaired ocular mobility and decreased visual acuity in both eyes. Palm X-ray imaging showed slight osteoporosis in both hands, but no arthritis. After detailed analyses, the function of the parathyroid gland was found to be normal and with the help of dynamic scintigraphy, we concluded that no changes in other bones of the body had occurred. Histopathology showed fibrotic hyperplasia with multiple giant multinucleated cells. She underwent the second surgical intervention in both jaws and the removal of teeth 31, 41, 33, 43, 72, 82.

In 2007, after discussion with a pathologist the final diagnose was defined as cherubism. Despite the diagnosis, as she had negative family anamnesis genetic testing was not performed.

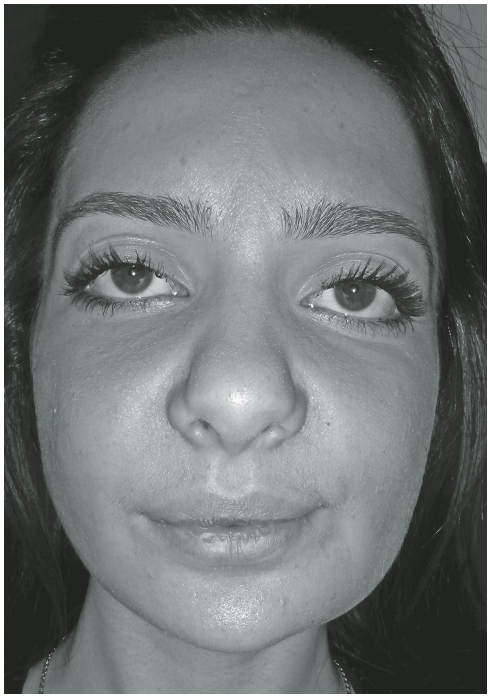

*Fig. 1. Physical appearance of the patient at the age of 16. Cherubism characterized by bilateral fullness of the cheeks and jaws with slight upward tilting of the eyes, giving a 'cherubic' appearance.*

Patient's monitoring and check-ups were performed every year until 16 years of age. Pathology was not evolving, formation of cysts stopped, but she ended up with a deformed jaw as she lost most of her teeth (Figure 2).

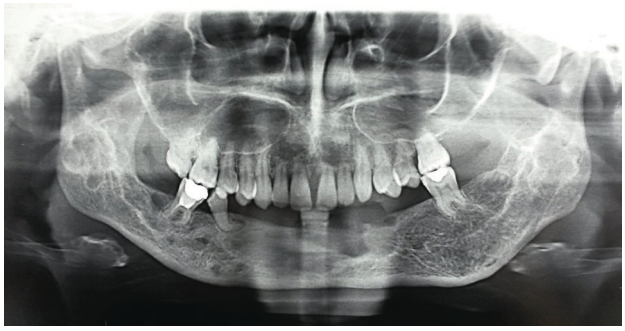

*Fig. 2. Orthopantomogram showing loss of teeth from the lower yaw.*

## Discussion

Cherubism is a germline autosomal dominant disorder with mutations in SH3BP2 gene affecting the jaws by replacing the bone with proliferated fibro vascular tissue containing multinucleated giant cells. Some cases are presented without familial histories.[6,7] It regresses spontaneously throughout the puberty, so the treatment ranges from wait-and-see principle to surgical reconstruction. In case of a defect resulting in difficulty with breathing, ocular visibility or chewing capacity, surgical intervention is encouraged. From the esthetic perspective the appearance might be traumatic for the patient so surgical procedure is still considered as the treatment of choice. In cases of continues tissue growth and expansion, several surgical interventions may be performed as this was also observed in our case report. Pharmacological intervention with calcitonin is another option but remains only as a suggestion due to limited clinical evidence.[8]

Cherubism more frequently affects the mandible, sometimes also the maxilla, and later it may extend to the orbital and palate bones. The difficulty of diagnosis in our case was that the patient was presented with cysts in the frontal region of the maxilla. Enlarged lymph nodes were noted in the submandibular region of the jaws and no ocular mobility or visual acuity was observed. The differential diagnosis at the time did not indicate cherubism. Although histopathological examination of the tissue showed giant cell granuloma, cherubism might include various syndromes such as multiple giant cell lesions, fibrous dysplasia, brown tumor of hyperparathyroidism, and ossifying fibromas with hyperparathyroidism-jaw tumor.[9] As maxillofacial surgeons we had difficulties at first to diagnose cherubism in our case. The patient had no family history, and we were not used to do a molecular testing with the detection of a mutation in the SH3BP2 gene in our everyday practice. Yet at the second visit, the progres-

sion of tissue and conversation with the pathologist helped us to establish the diagnosis of cherubism. Normally, clinical or radiographic findings of cherubism are not evident until the age of 14 months to 3 years, yet our patient was 11 years old when diagnosed with cherubism. Frequently, cherubism is accompanied by abnormalities in the dental arch and bones other than the jaws. Tooth resorption may also occur. The signs and symptoms of the disease depend on the severity of the condition, ranging from undetectable to deformed jaws and palate, impairment of breathing, vision and hearing or even death[7]. Biochemical investigations show normal limits of serum calcium and phosphorus concentrations, TSH, FSH, +LH, T4 and T3 levels but sometimes elevated levels of alkaline phosphatase.[5-8] Thus, blood parameters are not the best diagnostic tool as confirmed also by the case of our patient. She had clinical characteristics of cherubin face, symmetrical enlargement of the jaws, V arch-shaped palate, loss of teeth, lymphadenopathy, and hyperparathyroidism and her alkaline phosphate was within the normal range. Excluding morphological observations, the diagnosis was rather indicating grey tumor.

This shows that the diagnosis of cherubism is complex and should be based on a combination of clinical, radiological, and histological data. The clinical manifestations include family anamnesis, bilateral enlargement of the jaws, arch-shaped palate, loss of second and third molars, and recurrence of the disease, lymphadenopathy, spontaneous regress or complete stop of formation growth, lack of involvement of the temporomandibular joint. Radiographic manifestations include multiple cystic-lytic symmetrical lesions of the upper and lower jaw. Conducted CTs reveal honeycomb-like changes in the cortical layer of the lower jaw. In the upper jaw, CT shows defeat tuberosity with a lesion of the maxillary sinus and the elevation of the lower orbital floor. Histology discovers fibrotic hyperplasia with multiple giant multinucleate cells. In the phase of reparation, pseudo cystic changes are possible. Differential diagnosis is ruled out between fibrotic dysplasia, osteosarcoma, juvenile ossifying fibroma, osteoma, odontogenic cysts, and hyperparathyroidism. X-ray typically reveals a two-side lesion of the jaws with the presence of family cases and facilitates diagnosis without histological verification. However, observations of cases, such as ours, without hereditary character and the first appearance by the age of ten are described elsewhere.[4,10]

## Conclusion

Among rare reports on cherubism, this is one of additional case reports with sporadic cherubism in a young female patient without familial pattern. Initially due to disorder complexity cherubism was not established by the surgeons and was done due to condition progression. Fortunately, the condition did not cause significant facial deformity and or functional impairments. In several cases, cherubism is self-limiting, but this case proliferated at the second visit, so the patient underwent two surgical procedures.

## Ethical considerations

The work was approved by the Departmental Ethical Committee and performed in accordance with the Declaration of Helsinki. Authors certify that they have obtained all appropriate patient consent forms. The legal guardians have given their consent for images and other clinical information to be reported in the journal. The name and initial of the patient are not published and due efforts have been made to conceal the identity of the patient.

## Conflict of interest

Authors declare no conflict of interest.

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## PRIKAZ RIJETKOG SLUČAJA SPORADIČNE PONOVNE POJAVE KERUBIZMA: POTEŠKOĆE S GLEDIŠTA KIRURGA


### S A Ž E T A K

Kerubizam je rijetka koštana displazija u djece koju karakterizira simetrična resorpcija kosti ograničena na gornju i donju vilicu i dijagnosticirana kao koštane lezije ispunjene mekim vlaknastim tkivom bogatim divovskim stanicama, koje se mogu proširiti i uzrokovati ozbiljne deformacije lica. Većina pacijenata ima mutacije zametnih stanica u genu SH3BP2 koji je signalni adapterski protein uključen u adaptivne i urođene imunološke odgovore. Liječenje ovisi o kliničkom tijeku bolesti. Prikaz slučaja opisuje mladu bolesnicu s cistama u frontalnom predjelu maksile bez obiteljske anamneze, koja je imala recidive cista, a predstavlja slučaj manje dokumentiranog rijetkog poremećaja. Histološki nalaz je ukazivao na granulom divovskih stanica, a kasnije i na sivi tumor. Zbog postojanja drugih patoloških nalaza u čeljusti uz prisutnost divovskih stanica, mi smo kao kirurzi imali poteškoća u postavljanju dijagnoze kerubizma.