Cherubism.

by Lester D. R. Thompson, MD

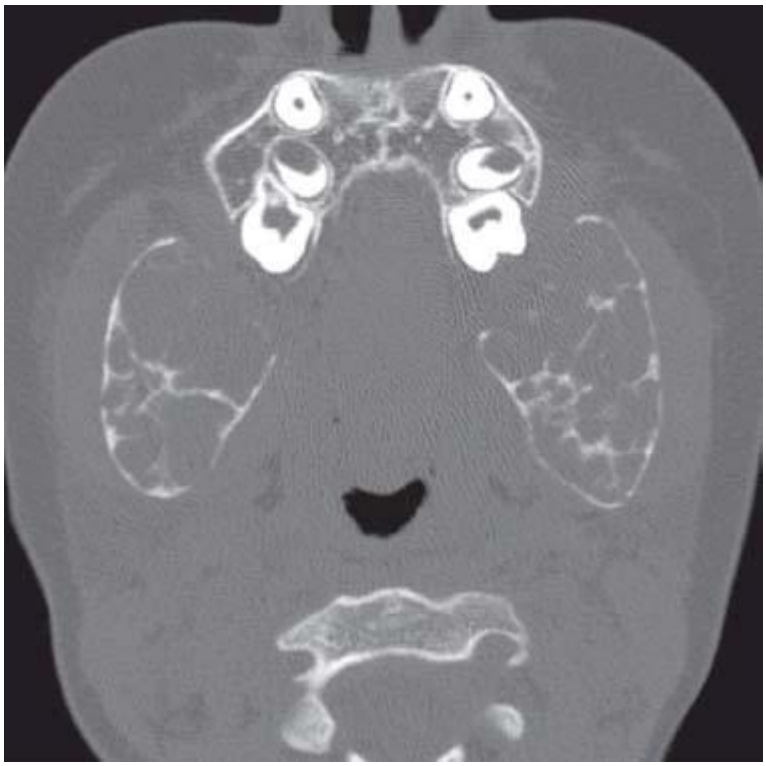
Cherubism is an autosomal-dominant inherited disease with variable expression. It is characterized by a progressive, painless, and symmetric expansion of the jaws. The disease is caused by a point mutation in the SH3BP2 gene (chromosome 4p16.3), which leads to dysregulation of the Msx-1 gene; this gene is involved in regulating mesenchymal interaction in craniofacial morphogenesis.

The disease is named for the resemblance of affected patients to cherubs; it manifests as a round face with an upward gaze (figure 1). This rare disease is usually identified within the first 2 years of life, and nearly always by the time the patient is 5 years old; another family member is often affected. It is twice as common in boys as in girls.

Figure 1. Illustration of a young boy with cherubism shows the prominent cheeks and upwardly gazing eyes. Reprinted with permission from Gannon FH, Thompson LD. Cherubism. In: Thompson LD, Wenig BM (eds). Diagnostic Pathology: Head and Neck. Altona, Manitoba, Canada: Lippincott Williams & Wilkinson; 2011:6/5.)

While the jaws can be affected bilaterally, the mandible is most commonly affected. The ascending rami and molar/retromolar areas are particularly prone to the disorder, while the condyles are spared. The disorder starts at the mandibular angle and then spreads to the ascending rami and body (figure 2).

Figure 2. Axial computed tomography in a patient with cherubism shows an expanded mandible with symmetric involvement by multiple cysts. There is bone expansion but not bone destruction.



Signs and symptoms vary significantly, depending on the severity of the condition (complete or incomplete penetrance), and they are quite nonspecific. Patients usually present with a symmetric, hard, and painless swelling of the jaws. The younger the age at presentation, the faster the lesion seems to expand.

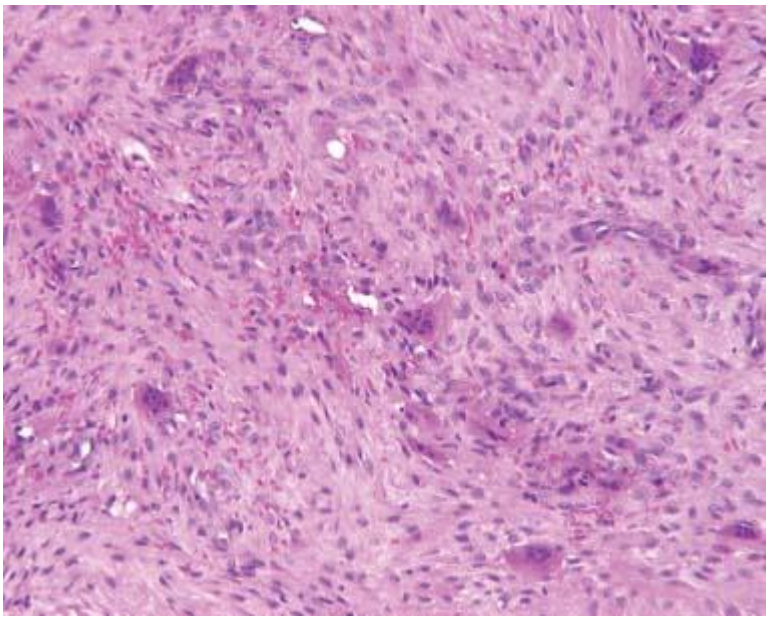
The overgrowth can result in a grotesque deformation of the facial bones and lead to respiratory distress and impaired vision and/or hearing. Specifically, when there is significant infraorbital maxillary involvement, the inferior rim of the sclera is more prominent, resulting in the classic “eyes to heaven” appearance (figure 1). Malaligned teeth may be seen. There is a rare association with Noonan, Ramon, and fragile X syndromes. Imaging demonstrates massive, bilateral multilocular radiolucent cystic areas within the gnathic bones (figure 2). However, in adults, multilocular rarefactions become sclerotic with progressive calcification.

The disease is characterized by the loss of bone in the jaws only; the lost bone is replaced by fibrous tissue. Unfortunately, without knowing the clinical and radiographic features, the histologic appearance is not diagnostic, so clinicopathologic correlation is required.

The lesions are unencapsulated and without a periosteum. Their consistency ranges from hard to semihard to soft and sometimes jelly-like. There is a highly vascular fibrous connective tissue stroma arranged in a storiform to whorled pattern, and it contains osteoclast-type multinucleated giant cells (figure 3). The fibroblasts can be quite large with prominent nucleoli. Perivascular hyalinization (collagen cuff) surrounds prominent vessels in most cases. With time,

bone remodeling can be seen, and there is no true bone formation. Polarization will show woven bone. These changes can also be seen in fibrous dysplasia, hyperparathyroidism, giant-cell tumor, and infantile cortical hyperostosis.

Figure 3. Giant cells are seen within a fibrous connective tissue stroma with prominent fibroblasts. This finding alone is nonspecific. for cherubism; clinical and/or imaging correlation is necessary to establish a diagnosis.



Watchful waiting is usually encouraged, as spontaneous involution, regression, or stabilization can occur during the teenage years. Maxillary lesions usually begin to regress earlier than do mandibular lesions. If there are major impediments to speech, chewing, swallowing, vision, or hearing, surgery may aid. However, early surgical intervention is contraindicated because it seems to predispose to recurrences. Radiation therapy is absolutely contraindicated because of the risk of osteoradionecrosis or fibrosarcoma. The patient's facial appearance may return to completely normal by the fourth or fifth decade of life. The vast majority of patients experience no residual disease.

Suggested reading

1. Flanagan AM, Speight PM. Giant cell lesions of the craniofacial bones. Head Neck Pathol 2014; 8 (4): 445-53.
2. Papadaki ME, Lietman SA, Levine MA, et al. Cherubism: Best clinical practice. Orphanet J Rare Dis 2012; 7 (Suppl 1): S6.
3. Reichenberger EJ, Levine MA, Olsen BR, et al. The role of SH3BP2 in the pathophysiology of cherubism. Orphanet J Rare Dis 2012; 7(Suppl 1):S5.

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