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Cherubism: A Case Report

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Abstract: Cherubism is a rare genetic disorder resulting in the replacement of the mandible and sometimes the maxilla with expansile cystic lesions. The disorder usually presents in childhood, with eventual quiescence in early adulthood. We report a case of cherubism involving both the mandible and the maxilla and complicated by mass effect on the nasal cavity and the left orbit. Pathologic features, clinical considerations, and treatment of cherubism are discussed.

Keywords: *cherubism, mandible, SH3BP2*

Key Points

- Cherubism is a genetic disorder that causes expansile cystic lesions affecting the mandible and maxilla.
- Cherubism is most often caused by a mutation in the *SH3BP2* gene (OMIM 602104) that is inherited in an autosomal dominant fashion.
- The radiologist's main role is to identify complications of cherubism, such as tooth impaction, sinus obstruction, and cranial nerve compression.

Case Presentation

A 6-year-old boy presented to the hospital with concern for a painless, expansile right-sided facial mass, which had been growing for approximately one year. The swelling was primarily over the right-sided mandibular ramus. Of note, the patient's mother also noticed the patient had swelling of the left side of the face over the mandible and the maxilla. The patient's medical history was significant for an incidental cystic hygroma and feeding intolerance at birth, which was unrelated to the development of the facial masses of concern. Physical examination revealed a large mass palpable intraorally over the right mandible. There was no evidence of loose teeth or infection, and there was no family history of similar lesions.

A computed tomography (CT) scan of the skull and the face revealed multilocular cystic expansile lesions within the posterior aspects of the mandible bilaterally and the left maxilla (Figure 1A). The maxillary lesion also exhibited mass effect on both the inferior left orbit and the nasal cavity, with subsequent proptosis and cortical thinning of the inferior orbital wall (Figures 1B and 2).

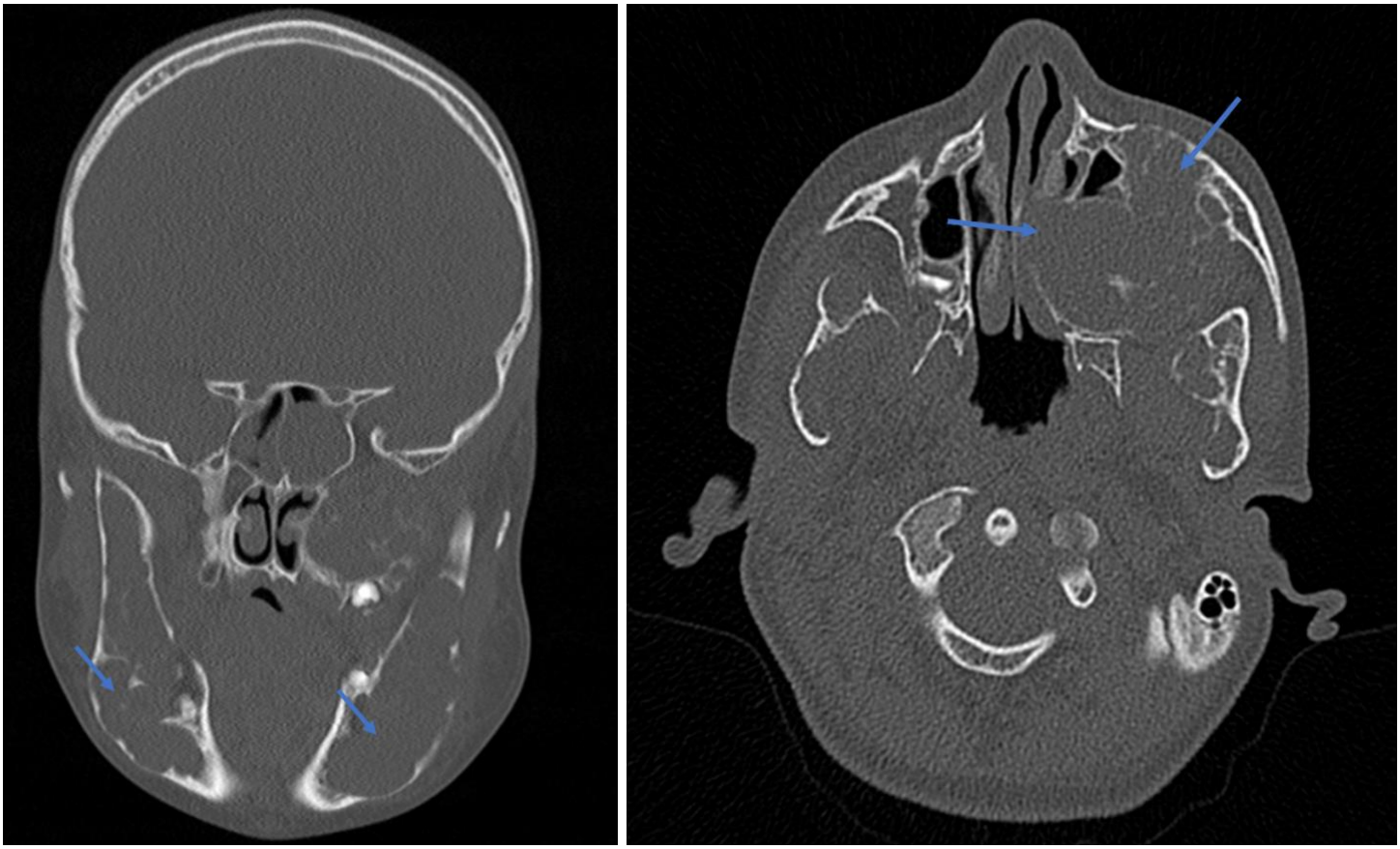
The patient then underwent surgical contouring of the right mandibular ramus and a biopsy of the lesion. The patient tolerated the procedure well and was discharged home on a soft food diet with feeding advancement as tolerated.

The histopathologic examination of the biopsied specimen revealed a cellular lesion made of spindle cells in a background of a fibrocollagenous tissue. Multinucleated osteoclastic giant cells were scattered throughout the lesion, and trabecular bone with osteoblasts was present at a periphery. These findings were consistent with a diagnosis of central giant cell granuloma secondary to cherubism. Genetic testing remained pending at the time of publication.

Figure 1. Computed Tomography (CT) of the Mandible and the Maxilla of a 6-Year-Old Boy.

A CT, coronal view

B CT, axial view



(A) CT, coronal view, through the mandible on the bone window shows large lytic lesions extending throughout the mandible (blue arrows). While these findings are highly suggestive of cherubism, they are not pathognomonic for the disorder. (B) Axial CT at the level of the maxillae illustrates lesions in both the mandible and the maxilla (blue arrows).

Discussion

Etiology

Cherubism is a rare genetic disorder most commonly acquired in an autosomal dominant fashion.[1] The cherubism locus was mapped to chromosome region 4p16.3, with missense mutations in the gene encoding protein *SH3BP2* (OMIM 602104).[2] This gene is expressed in the multinucleated giant cells and stromal cells found within classic cherubism lesions.[3] This mutation has been found in 93.5% of reported cases.[2]

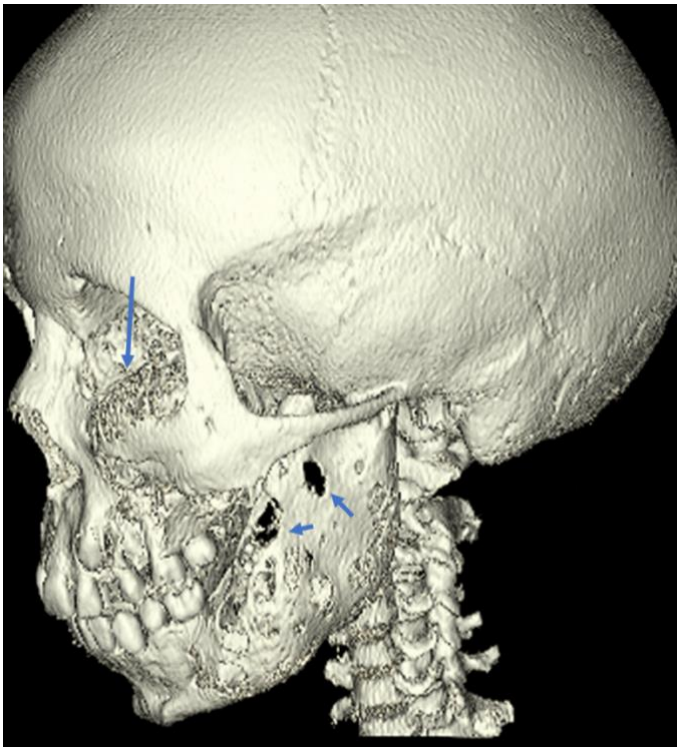
Pathology

Osteoclasts are the primary histological feature of cherubism. In one case series, all patients exhibited a replacement of bone with fibrous tissue containing embedded mature fibroblasts as well as multinucleated giant cells.[4] These findings are consistent with the case presented here (Figure 3). Cytologic features of cherubism are not commonly described, but the results of one fine-needle aspiration demonstrate bland cells with a normal nuclear-to-cytoplasm ratio and unremarkable chromatin.[5] These features, however, are not unique to cherubism, as other disorders, such as giant cell tumors, may also include them. An additional defining feature, which occurs in about 28% of cases, may be eosinophilic cuff-like perivascular deposits.[2]

Radiographic Features

The primary radiologic modalities for evaluating cherubism are radiography and computed

Figure 2. 3D Reconstruction of the Skull of a 6-Year-Old Boy.

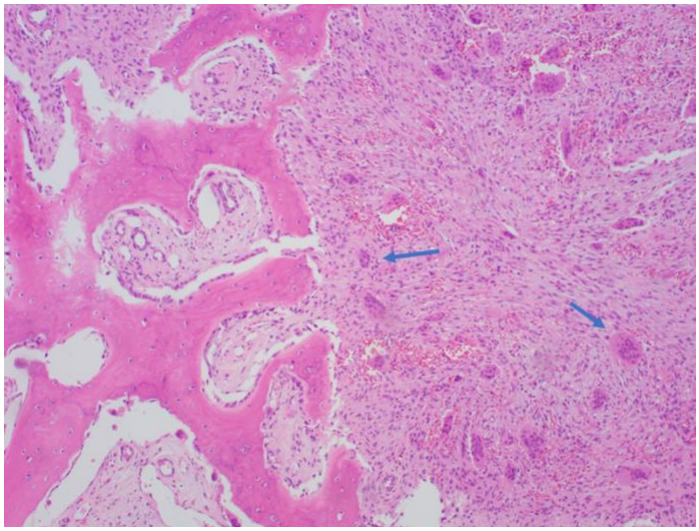


3D reconstruction demonstrates multiple multilocular lucent lesions involving the left mandible and maxilla (blue arrows).

tomography (CT). On panoramic radiographs, cherubic lesions are typically bilateral, multilocular, and radiolucent and are often found in the mandibular angle with spread to the remaining parts of the mandible. Lesions may also arise in the maxillary bones and other facial bones. Computed tomography of the face and the orbits can further delineate the lesions and identify common complications, including orbital or sinus involvement and tooth impaction. In addition, CT can identify regions of periosteal reaction, cortical thinning, and trabeculation.[6] In their cross-sectional study, Redfors et al[7] identified osteosclerosis in all 11 of their patients, with cortical abnormalities present in 7 patients. On magnetic resonance imaging, lesions are classically described as homogeneously isointense to skeletal muscle on T1-weighted images and heterogeneously hypointense on fast spin-echo T2-weighted images with fat suppression.[8]

While large radiolucent lesions in the jaw are highly suggestive of cherubism, they are not pathognomonic of the disease. The primary considerations for radiologic differential diagnosis should include fibrous dysplasia, giant cell tumor, brown tumors of hyperparathyroidism, Langerhans cell histiocytosis, and familial gigantiform cementoma.[6,8] Bilateral symmetry of lesions would be extremely rare in patients with fibrous dysplasia or giant cell tumor, and these patients tend to be older at the age of onset than patients with cherubism.[6] Hyperparathyroidism is also rare in childhood, and patients with cherubism do not have the abnormal levels of parathyroid hormone, calcium, phosphorus, and alkaline phosphatase typical of hyperparathyroidism.[9] Langerhans cell histiocytosis would be more likely than cherubism to cause painful lesions that may result in pathologic fractures; ultimately, tissue biopsy and histopathologic examination can help differentiate between this entity and cherubism.[6,8] Finally, familial gigantiform cementoma is characterized by cementum production in bone lesions. However, this tends to predominate in the maxilla rather than the mandible, and again, biopsy can be used to clarify the diagnosis. [6,8]

Figure 3. Digital Pathology Slide of Maxilla Resection Specimen Hematoxylin & Eosin (H&E) Stain; 10x Magnification.



The marrow space is replaced by a bland proliferation of fibroblasts, which are replacing bone (left). Present in the fibroblastic areas are disease-associated multinucleated giant cells (blue arrows), typical of this condition.

Clinical Considerations and Treatment

Because of the rarity of the disease,[9] there is a general lack of information available regarding cherubism and of its definitive treatment

guidelines. While the most common trajectory of the disorder involves painless development of lesions starting around the age of 2-7, with lesion quiescence and regression occurring in young adulthood, [9] every case is unique, with varying levels of pain and continued development throughout adulthood.[7,9,10]

The radiologist plays an important role in identifying the complications associated with cherubic lesions. Dental complications are one of the most prevalent issues in cases of cherubism, with tooth displacement occurring in approximately 95% of cases.[2] Complete tooth agenesis is another common complication.[2,9] Orbital involvement is also prevalent,[9] as was observed in our case, with lesion expansion into the orbital floor resulting in proptosis and involvement of the inferior rectus muscle causing the eye to tilt upwards. Cherubism can also result in dysphagia and obstructive sleep apnea.[9] Particularly severe cases have resulted in vision loss and decreased extraocular muscle motility due to optic neuropathy from optic nerve compression.[9] Airway obstruction can lead to pulmonary infections, sepsis, and even death. [9]

Treatment approaches vary but are generally conservative.[9] Most cases, such as the one presented here, only escalate to surgical intervention after the development of complications such as nasal obstruction, dental impaction, and proptosis.[9] In limited case series, calcitonin, bisphosphonates, and tacrolimus were used with varying success in the control of lesion growth.[9] Radiation therapy was used in the past but is now contraindicated because of concerns for jaw osteonecrosis and an increased risk for iatrogenic development of malignant tumors. [9]

Conclusion

We report a case of cherubism affecting a 6-year-old boy. With few reported cases of cherubism in the literature, diagnostic and treatment guidelines are not definitive. A combination of radiologic and histopathologic investigation can provide better opportunity for diagnosis than either modality alone. Radiologic investigation is particularly well-suited for the identification of complications, such as the orbital involvement, caused by cherubism.

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Author Contributions

Conceptualization, M.A.M. and N.S.; Acquisition, analysis, and interpretation of data, M.A.M. and J.P.; Writing – original draft preparation, M.A.M.; Review and editing, M.A.M. and N.S.; Supervision, N.S. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Disclosures

None to report.

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