Regional Lymph Node Enlargement in Clinically Severe Cherubism

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ABSTRACT: Cherubism is a rare benign autosomal dominant disorder characterized by progressive, painless, bilateral enlargement of the mandible and/or maxilla because of bone replacement by fibrotic stromal cells and osteoclast-like cells forming multilocular cysts. The lesions typically stabilize and regress after puberty. We present a 14-year-old male with severe familial cherubism. Bilateral mandibular enlargement began around age 4 and progressed until puberty, affecting his speech and mastication without subsequent involution. Composite mandibulectomy and mandible reconstruction with fibula free flap technique improved functionality and cosmesis. Histology was consistent with the diagnosis of cherubism, showing large areas of bland spindle-cell fibrous tissue and moderately abundant collagen and multiple nodules of giant cell-rich tissue resembling central giant cell granuloma. Regional lymph nodes were sampled due to enlargement, demonstrating hemosiderin-laden macrophages and basophilic laminated concretions localized to the cortical interfollicular space and along the peripheral follicular marginal zone, findings which have not been previously reported.

KEYWORDS: Cherubism, regional lymph node enlargement, hemosiderin-laden macrophages, basophilic laminated concretions, mandible

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Introduction

Cherubism (OMIM number 118400), also known as familial fibrous dysplasia of the jaws or familial multilocular cystic disease of the jaws, is a rare benign autosomal dominant genetic disorder characterized by progressive, painless, bilateral enlargement of the mandible and/or maxilla because of bone replacement by fibrotic stromal cells and osteoclast-like cells forming multilocular cysts.[1] The jaw lesions typically stabilize and will classically regress after puberty.[1] This disease is caused by a gain-of-function mutation in the *SH3BP2* gene encoding for the signaling adapter SH3-domain binding protein 2 (SH3BP2) mapped to the chromosomal locus 4p16.3.[2] The clinical presentation of cherubism is highly variable, even within a family, ranging from subclinical or limited enlargement of the mandible and maxilla to severe overgrowth with aesthetic, respiratory, and speech problems; impaired vision; and hearing.[3] The radiologic findings of cherubism are characterized by bilateral relatively symmetric jaw involvement that is limited to the maxilla and mandible, showing expansile remodeling of the involved bones, thinning of the cortexes, and multilocular radiolucencies with a coarse trabecular pattern.[3–5] Here, we present the case of a 14-year-old male with clinically severe familial cherubism, with the disease also affecting the patient's sister, father, and paternal grandmother. Although literature reviews note regional lymphadenopathy, to our knowledge, our article will be the first to address the pathologic findings of the lymph nodes associated with this disease entity.

Case Report

A 14-year-old male presented with bilateral mandibular enlargement beginning around age 4 with progression until puberty, with the disease affecting his speech and mastication. This enlargement did not subsequently involute or regress (Figure 1A). Computed tomography (CT) shows expansile osseous remodeling with multilocular appearance and coarse trabecular pattern of the mandible, prominent dental derangement involving the mandible, without orbital involvement or clear involvement of the maxilla, although there is mild derangement of the maxillary teeth (Figure 1B). Multiple bilateral enlarged regional lymph nodes are noted (Figure 1C). This disease also affects the patient's sister, father, and paternal grandmother.

Composite mandibulectomy and mandible reconstruction using the fibula free flap technique were performed to improve functionality and cosmetics. Gross examination of mandible resection specimen shows a 15 cm × 15 cm × 4 cm deformed mandible with focal cystic defects on the exterior

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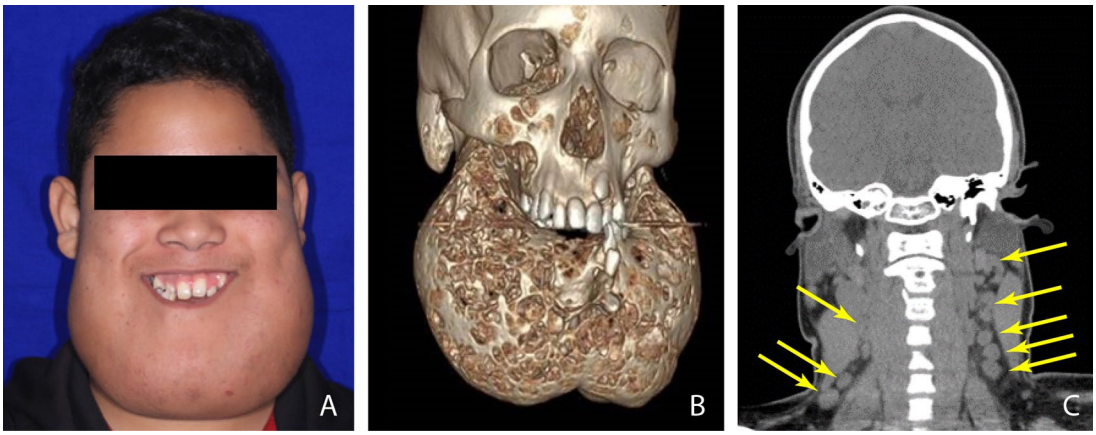

Figure 1. A 14-year-old male presented with bilateral mandibular enlargement and affecting his speech and mastication, and this enlargement did not subsequently involute or regress (A). CT shows expansile osseous remodeling with multilocular appearance and coarse trabecular pattern of the mandible, prominent dental derangement involving the mandible, without orbital involvement or clear involvement of the maxilla (B). Multiple bilateral enlarged regional lymph nodes are noted in CT as well (arrow) (C). CT indicates computed tomography.

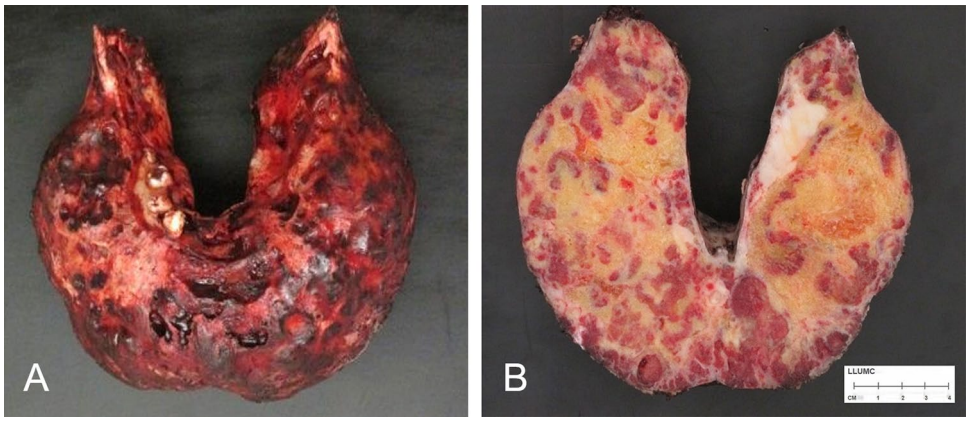

Figure 2. Gross examination of mandible resection specimen shows 15 cm × 15 cm × 4 cm deformed mandible with focal cystic defects on the exterior surface, poorly aligned premolar and molar teeth, and soft yellow tissue interspersed with patchy hemorrhage and solid white bone (A and B).

surface, poorly aligned premolar and molar teeth, and soft yellow tissue interspersed with patchy hemorrhage and solid white bone (Figure 2A and B). Histological examination of the mandible was consistent with the clinical diagnosis of cherubism, showing large areas of bland spindle-cell fibrous tissue with perivascular eosinophilic fibrin cuffing, moderately abundant collagen, and multiple nodules of giant cell-rich tissue resembling a central giant cell granuloma (Figure 3A and B). The mandible lesion also shows focal areas of hemosiderin deposition and calcification (Figure 3C and D). Regional lymph nodes were also sampled for interoperative consultation due to enlargement (2.3 cm × 2.0 cm × 0.5 cm) (normal lymph node size <1 cm),[6] and these demonstrated hemosiderin-laden macrophages and basophilic laminated concretions primarily localized to the cortical interfollicular space and along the periphery of the follicular marginal zone, findings which have not been previously reported in the literature for this disease (Figure 4A and B). The patient is doing well after surgery with improved speech and mastication and is being followed up regularly.

Discussion

Approximately 80% of patients with cherubism have been found to have a presumed gain-of-function mutation in the *SH3BP2* gene, which encodes the SH3-domain binding protein 2.[2] Cherubism is believed to result from presumed gain-of-function variants in SH3BP2 that alters the bone quality and reduces osteoblast function.[7,8] This protein is known to have several functions, including the regulation of transcriptional activity in several lineages of inflammatory cells and the regulation of differentiation and maturation of osteoclasts.[9,10] For example, a mouse model for cherubism demonstrated that the *SH3BP2* mutation in myeloid cells increased responses to M-CSF and RANKL stimulation, resulting in bone resorption caused by hyper-reactive osteoclasts and inflammatory reactions caused by hyper-reactive macrophages that increase cytokine tumor necrosis factor α (TNF-α) production.[9,10] The combination of inflammation and bone loss likely leads to the cyst-like lesions that characterize this disease. Based on the age of onset and the localized but bilateral disease presentation, it is speculated that the signaling

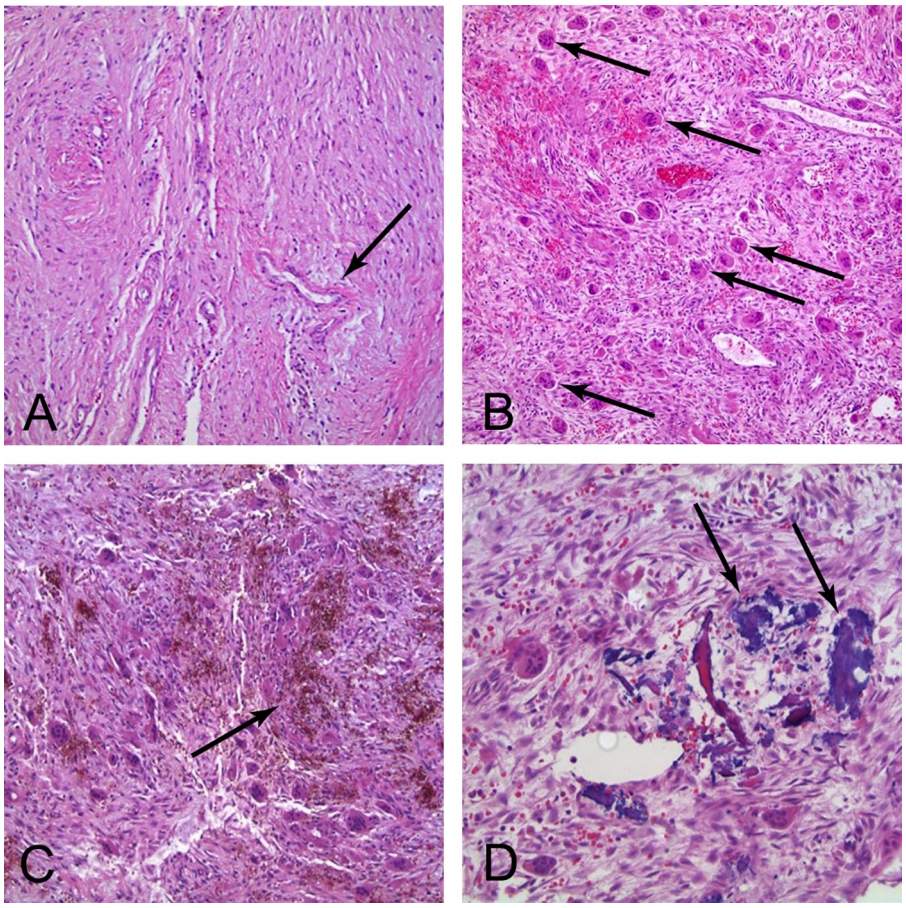

Figure 3. Histological examination of the mandible showed large areas of bland spindle-cell fibrous tissue with perivascular eosinophilic fibrin cuffing (arrow), with moderately abundant collagen and multiple nodules of giant cell-rich tissue (arrow) resembling a central giant cell granuloma (A and B). The mandible lesion also shows focal areas of hemosiderin deposition (arrow) and calcification (arrow) (C and D).

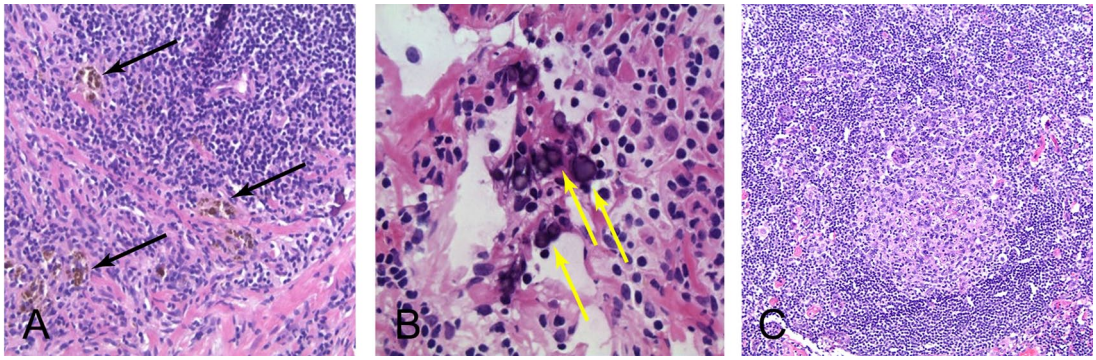

Figure 4. Regional lymph nodes demonstrated hemosiderin-laden macrophages (arrow) and basophilic laminated concretions (arrow) primarily localized to the cortical interfollicular space and along the periphery of the follicular marginal zone (A and B). A normal lymph node is shown in (C) for comparison.

molecules and cytokines associated with tooth eruption also play a key role in pathogenesis, though precise mechanisms have not yet been elucidated.[9,11,12] There are few case reports showing the association between cherubism and odontogenic neoplastic lesions, including central odonto-genic fibroma and odontogenic carcinoma, which suggests a relationship between cherubism with disturbed odontogenesis. In our patient, odontogenic epithelial components were not identified by morphology or by pancytokeratin immunostain (data not shown).[13,14]

Submandibular and cervical lymph nodes are frequently enlarged during early stages of cherubism.[3] Meng et al[5] reported that the lymphadenopathy was observed in 10 out of 24 patients with cherubism. Reports suggest that submandibular lymph nodes are enlarged during swelling of the lower portions of the face while upper cervical lymph nodes are involved when maxillary swelling occurs.[15,16] The cause of lymphadenopathy in cherubism has not yet been precisely characterized. Previously, the frequently described painless enlargement of the submandibular lymph nodes in

cherubism is thought to be a possible physiologic hyperplasia and fibrosis that are often found in other children as well.[17,18] However, current studies showed that it is speculated to be related to the inflammatory nature of the disease and to the bone resorption caused by hyperactive osteoclasts.[3,9,12] One possible theory could be that the cytokines and the hypersensitivity of myeloid cells trigger a self-sustaining loop of TNF-α expression that leads to osteoclastogenesis, soft fibrous tissue proliferation, and swollen lymph nodes.[9] Our findings of mineralized concretions within both the fibrous mandibular lesion and in the regional lymph nodes may be related to the pathologic bone resorption process and could provide support for the notion that this process contributes to the lymphadenopathy. Our hypothesis is that the overactive osteoclasts induce remodeling, reconstruction, and resorption of bone, and later osteoblasts will induce bone formation including bone mineralization. The bone mineralization may explain the presence of mineralized concretions. It does not have lamination which differ from psammomatous bodies. Dystrophic calcification occurs with the presence of adjacent degenerative cellular components, necrosis, or apoptotic cells, which are not identified in our case.

Treatment often varies depending on the disease presentation and severity. As most cases will ultimately spontaneously regress, "watchful waiting" is frequently cited as the preferred approach.[3] However, surgical curettage of the fibrous lesions or even jaw resection and reconstruction may be indicated in severe cases.[3] There have been several case reports of successful medical treatment using a calcineurin inhibitor, which down-regulates osteoclastic activity and has immunosuppressive activity.[19] Further studies will be needed to assess this treatment's effectiveness in other patients.

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Author Contributions

First draft, data collection, manuscript revision: YCW.
Data collection, manuscript review and revision: DJ.
Data collection, manuscript review and revision: JCI.
Manuscript review and revision: FA, CC and CWZ.
Supervision, manuscript review and revision: AR.

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