Bone 52 (2013) 347–353

Contents lists available at SciVerse ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Case Report

Anti-tumor necrosis factor treatment in cherubism — Clinical, radiological and histological findings in two children ☆

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ARTICLE INFO

Article history:
Received 22 August 2012
Revised 3 October 2012
Accepted 4 October 2012
Available online 12 October 2012

Edited by: David Fyhrie

Keywords:
Cherubism
Tumor necrosis factor α
Adalimumab
SH3-binding protein 2

ABSTRACT

Cherubism is a rare and disfiguring genetic disorder with excessive bone resorption and multilocular lesions in the mandible and/or maxilla. The disease-causing gain-of-function mutations in the SH3-binding protein 2 (SH3BP2) gene result in increased myeloid cell responses to macrophage colony stimulating factor and RANK ligand, formation of hyperactive osteoclasts (giant cells), and hyper-reactive macrophages that produce excessive amounts of the inflammatory cytokine tumor necrosis factor α (TNF-α). Recent findings in the cherubism mouse model suggest that TNF-α plays a major role in disease pathogenesis and that removal of TNF-α prevents development of the bone phenotype.

We treated two children with cherubism with the TNF-α antagonist adalimumab for approximately 2.5 years and collected extensive clinical, radiological and histological follow-up data during the treatment. Histologically the treatment resulted in a significant reduction in the number of multinucleated giant cells and TNF-α staining positivity in both patients. As evaluated by computed tomography and magnetic resonance imaging, the lesions in Patient 1 showed either moderate enlargement (mandibular symphysis) or remained stable (mandibular rami and body, the maxilla). In Patient 2, the lesions in mandibular symphysis showed enlargement during the first 8 months of treatment, and thereafter the lesions remained unchanged. Bone formation and resorption markers remained unaffected. The treatment was well tolerated.

Based on our findings, TNF-α antagonist may decrease the formation of pathogenic giant cells, but does not result in lesion regression or prevent lesion expansion in active cherubism. TNF-α modulator treatment thus does not appear to provide sufficient amelioration for patients suffering from cherubism.

Introduction

Cherubism (OMIM #118400) is a rare genetic skeletal disorder characterized by bone degradation and multilocular lesions in the mandible and/or maxilla, resulting in painless bilateral enlargement of upper and lower jaws. Clinical findings usually become apparent in early childhood, progress until puberty, and stabilize and regress after puberty [1]. Cherubism typically results in tooth displacement, facial disfigurement, and in severe cases, upper airway obstruction or vision disturbances due to pressure caused by lesion(s) protruding into the orbital cavity [2,3]. Bones other than the mandible and maxilla are usually not affected. Histologically the lesions contain fibrous tissue and osteoclast-resembling giant cells; hemosiderin deposits and sometimes cuff-like collagen deposits surround vascular spaces. The histological findings resemble the appearance of giant cell granulomas. Radiographs show soap-bubble like cystic lesions in the affected areas. Diagnosis is based on clinical, radiological and histological features [4,5].

No effective pharmacotherapy for cherubism is presently available, and the treatment is supportive. Orthodontic treatment is usually required, and surgical intervention is often necessary for severe functional disturbances.

Cherubism is an autosomal dominant disease mapped to choromosome 4p16.3 [6] and in most cases it is caused by gain-of-function

☆ This study was supported by the Sigrid Juselius Foundation; the Foundation for Pediatric Research; the Academy of Finland; and the Folkhälsan Research Foundation, all Helsinki, Finland.

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http://dx.doi.org/10.1016/j.bone.2012.10.003

mutations in the SH3-binding protein 2 (SH3BP2) gene [7]. According to recent studies in a homozygous knock-in mouse model with Pro416Arg mutation in the *SH3BP2* gene (corresponding to the typical human cherubism mutation Pro418Arg), cherubism mutations result in increased stability and levels of SH3BP2, caused by loss of recognition and destruction of the protein by Tankyrase [8,9]. SH3BP2 is an intracellular adaptor protein, which plays a crucial role in hematopoietic cell differentiation and function [10], and positively regulates the activity of the nuclear factor of activated T cells c1 (NFATc1), a key regulator of osteoclastogenesis [11]. Based on findings in the cherubism mouse model, the bone phenotype results from increased myeloid cell responses to macrophage colony stimulating factor (M-CSF) and RANK ligand (RANKL) [12]. This excessive myeloid cell stimulation leads to the development of hyperactive osteoclasts (giant cells) with high bone-resorbing activity, and hyperactive macrophages that produce excessive amounts of tumor necrosis factor alpha (TNF-α). This in turn stimulates M-CSF and RANKL production [13]. Increased TNF-α production by macrophages appears to have an essential role in disease pathogenesis; when the knock-in "cherubism" mice were crossed with TNF-α null mice, no bone loss or inflammation occurred [12]. Thus, based on this animal model, cherubism has inflammatory characteristics and TNF-α is required for the development of cherubism-associated bone loss [12].

We hypothesized that blockade of TNF-α might ameliorate the course of this mutilating disease. We treated two patients with typical cherubism phenotype and *SH3BP2* mutations with TNF-α antagonist for approximately 2.5 years and collected extensive clinical, radiological and histological follow-up data during the treatment.

Patients and methods

Patients

The decision to start adalimumab, a TNF-α antagonist, in our two patients was based on thorough evaluation by a multidisciplinary team of potential risks and benefits of such treatment, and of the disease severity in individual patients. Before the start of the therapy, patients and their guardian(s) were informed about the potential risks and experimental nature of the treatment in this condition. The Hospital Research Ethics Committee approved the data collection and analysis from hospital records.

Patient 1 is a boy who was first evaluated by a dentist for painless bilateral cheek swelling at age 4.4 years (Fig. 1A). Panoramic radiograph (Fig. 1B) and computed tomography (CT) scans showed bilateral, multilocular, expansile radiolucencies with cortical thinning and destruction in the ramus, angulus and corpus of both sides of the mandible. Similar lesions were also noted in the maxilla without orbital involvement. Dental age was within the normal range. In the panoramic radiograph the developing tooth germs for the second and third molars and mandibular second premolars were not visible. The roots of lower primary second molars and left primary first molar showed premature resorption; in addition, the primary canine in the left side of the mandible had exfoliated prematurely. Bone biopsy from the mandible was consistent with giant cell granuloma. Based on clinical, radiological, and histological findings, the diagnosis of cherubism was set. Thereafter, the patient has been followed up by surgeons and orthodontists. During the follow-up increasing swelling of both the maxilla and mandible was seen. The changes of the facial contour were more prominent and as the patient was suffering from these changes we decided together with his guardians to start the TNF-α antagonist treatment at the age of 7.3 years.

Patient 2, a girl, was first evaluated by a dentist at 4.5 years for expansion of the symphysis of the lower jaw (Fig. 1C). Panoramic radiograph (Fig. 1D) revealed bilateral multilocular, expansile radiolucencies of the mandible, particularly in the symphysis mandibulae; the findings were subsequently confirmed by CT. In addition, milder maxillary involvement in the tuberosity areas and obvious tooth displacements particularly in the mandible were visible. Biopsy confirmed giant cell granuloma and the diagnosis of cherubism. The dentition of the patient was also severely affected with cherubism. The roots of the lower primary deciduous

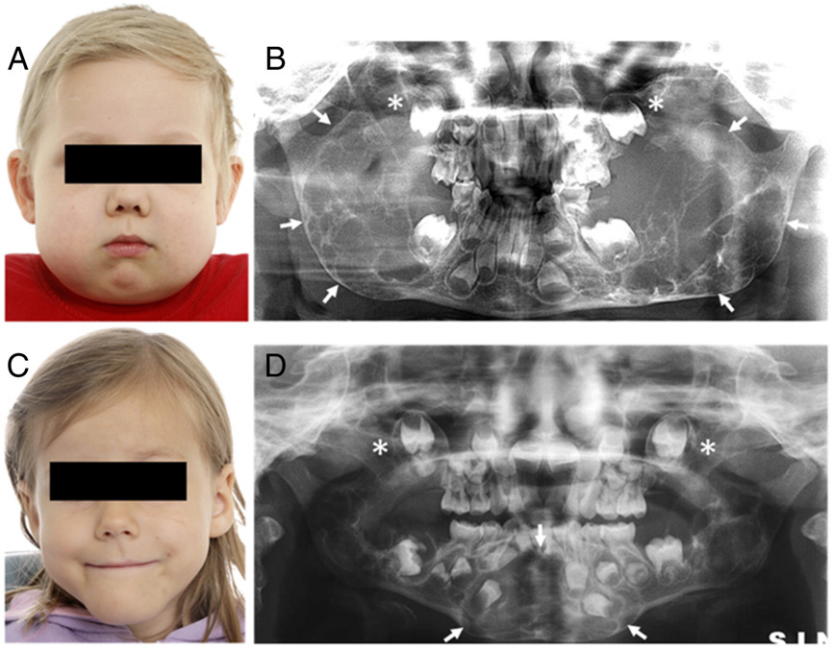

Fig. 1. Pretreatment photographs and panoramic radiographs of the two patients with cherubism at the time of diagnosis. A–B: Patient 1 at age 4.4 years with extensive bilateral expansile radiolucent lesions with cortical thinning and bone destruction in the rami and bodies of the mandible (arrows) and maxillary tuber regions (asterisks). Displacement of the developing permanent lower first molars and the upper right permanent molar caused by the lesion was observed. In addition the tooth buds of the second lower premolars are not normally visible. C–D: Patient 2 at age 4.5 years with bilateral multilocular expansile mandibular radiolucencies particularly in the symphysis region (arrows). Also maxillary tuberosity is bilaterally affected (asterisks). Obvious displacement of the developing teeth caused by the lesion is visible particularly in the parasymphysis regions.