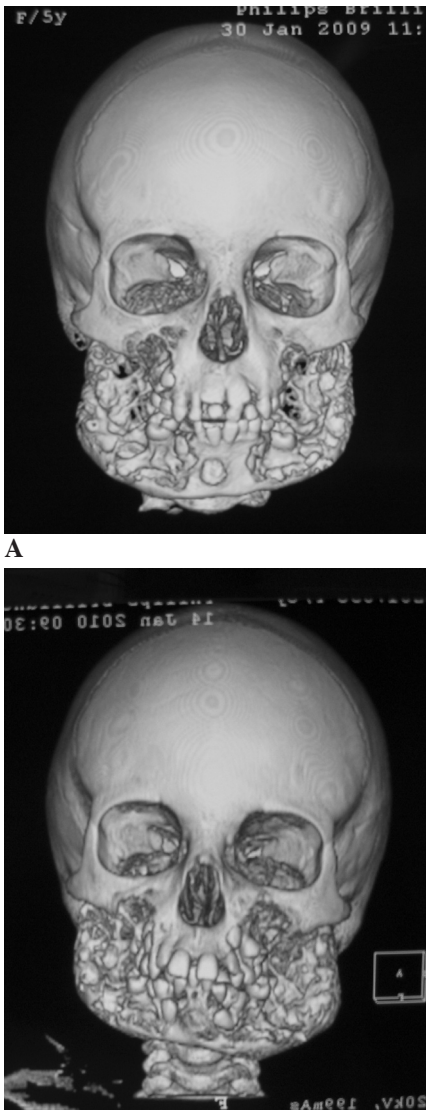
Ineffectiveness of tumour necrosis factor-alpha inhibition in association with bisphosphonates for the treatment of cherubism

Sirs,

Cherubism (OMIM 118400) is a rare genetic disease clinically characterised by symmetrical painful swelling of mandibles and maxilla, secondary to multilocular cysts composed of fibrotic stromal and osteoclast-like cells. It is transmitted as an autosomal dominant disorder, has its onset in early childhood, and clinical manifestations (that include upward gaze and dental abnormalities) usually stabilise around puberty. Diagnosis is based on family history and clinical findings, although a genetic defect has been found (missense mutations in the SH3BP2 gene on chromosomal locus 4p16.3) (1-3). Treatment of cherubism in humans is unsatisfactory and mainly based on surgical procedures. Although the disease is usually self-remitting and not life-threatening, it is cause of significant cosmetic as well as functional problems, and frequently patients need multiple surgical procedures and suffer from psychological consequences.

We recently encountered a family in which mother and daughter were affected by this condition. The mother asked us for treatment for the affected daugther since the disease had an extensive impact on her life. Since osteoclasts seem to play a major role in this condition (4-7) and bisphosphonates exert their antiosteoporotic effects mainly by inducing osteoclast apoptosis, we decided to start a trial with an oral bisphosphonate. Moreover, we also added the TNF-inhibitor adalimumab to the therapeutic regimen. In fact, as in mice, human jaw lesions are inflammatory lesions "driven" by high local levels of macrophage-produced TNF-alpha, and in the animal model, inflammatory infiltrates and most of the bone loss can be eliminated in the mice by removing TNF-alpha (8).

A 5-year-old girl, born from a twin pregnancy from non-consanguineous parents, presented to our observation for painful swelling of the cheeks that had been present and progressive since the age of 3. She also presented upward gaze and poor decidual dentition. Her twin sister was healthy, while her mother had been suffering from the same signs since the age of 2, and had been subjected to multiple surgeries, with important psychological consequences. The diagnosis of cherubism had already been made, both for the mother and daughter, on the basis of the typical clinical appearance. No genetic analysis was performed since the diagnosis was obvious, clinically. At physical examination, the young girl was in general good health and no abnormalities except the cranial ones were evident. Radiographs of the jaw showed bone fibrous dysplasia with signs of malocclusion. A head CT scan with tridimensional reconstrunction showed thick jaw cortex, multilocular cysts, a bulging and blown appearance of jaw branches, with involvement of the zygomatic-malar structures and posterior walls of maxillary sinuses. Since the disease was progressing and the mother was requesting a therapeutic trial in order to prevent further progression, we started treatment with alendronate (35 mg/weekly orally) and adalimumab, a monoclonal humanised anti-TNF-alpha antibody (24 mg/m^2/every two weeks subcutaneously). Ethics committee approval from our institution and written informed consent from the mother were obtained.



A

B

Fig. 1. Frontal views of the CT scan showing no improvement (**A**, before, and **B**. after treatment).

Treatment was well tolerated, but after 9 months of treatment, the girl came back to our attention for evaluation of effectiveness of therapy. Unfortunately, clinical examination and CT scan did not show an improvement. If anything, a slight progression was noted (Fig. 1). We therefore decided that therapy could be discontinued for ineffectiveness. Six moths after discontinuation, the disease had continued to progress at the same rate as before and during treatment. We acknowledge the limits of a single case report, however, we think it is of interest the fact that, despite hopes based on experimental evidence, treatment of cherubism with a 9-month course of anti-TNF and alendronate was not effective in our patient.

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