Case Report
Cherubism misdiagnosed as giant cell tumor: a case report and review of literature

Yang Jiao1*, Mi Zhou1*, Yaowu Yang2, Jun Zhou3, Xiaohong Duan1

1State Key Laboratory of Military Stomatology, Department of Oral Biology, Clinic of Oral Rare Diseases and Genetic Disease, School of Stomatology, The Fourth Military Medical University, Xi’an, P. R. China; 2State Key Laboratory of Military Stomatology, Department of Oral and Maxillofacial Surgery, School of Stomatology, The Fourth Military Medical University, Xi’an, P. R. China; 3State Key Laboratory of Military Stomatology, Department of Pathology, School of Stomatology, The Fourth Military Medical University, Xi’an, P. R. China. *Co-first authors.

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Abstract: Cherubism is characterized by progressive, painless, bilateral enlargement of the mandible and/or maxilla resulting from the replacement of bone with multilocular cysts composed of fibrotic stromal cells and osteoclast-like cells. Here we report one Chinese cherubism case that has been misdiagnosed for more than forty years. The patient displayed no typical clinical or radiographical signs of cherubism due to multi-surgical treatments. Her histopathologic examination revealed the proliferating fibrous connective tissue with few multinucleated giant cells. The family history suggested us to perform sequence analysis of the SH3BP2 gene, a candidate marker for cherubism, in the family, and it was found that both the proband and the son had a missense mutation in SH3BP2 in exon 9 (p. Arg415Gln). Here we emphasize the importance of gene testing in the diagnosis of suspected cherubism, especially for those cases with non-typical clinical, radiographic and histological presentations.

Keywords: Cherubism, SH3BP2, diagnosis

Introduction
Cherubism (OMIM, 118400) is an autosomal dominant hereditary disease firstly described as “familial multilocular cystic disease of the jaws” by Jone [1, 2]. It is characterized by progressive, painless expansion of mandible and/or maxilla, upward cast of the eyes, leading to the resemblance to the cherubs in Renaissance art [3-6]. Recently isolated non-familial cases have also been reported [7-9]. Cherubism has a penetrance of approximately 100% in males and 50%-75% in females [10-12]. The diagnosis of cherubism can be difficult for those cases with non-typical clinical and radiographic signs. Multi-surgical treatments may also challenge the diagnosis of cherubism.

Here we report one Chinese cherubism case with a complex medical history of being misdiagnosed for more than forty years. We also reviewed the recent literatures about the diagnosis, differential diagnosis, as well as the genetic testing of cherubism.

Case report
A 57-year-old female visited the outpatient center of the Department of Oral and Maxillofacial Surgery, School of Stomatology, the Fourth Military Medical University with the complaint of a painless enlargement of her left face for sixteen years. The patient first noticed the bilateral swelling of her face when she was in elementary school. The size of the lesion was increased gradually afterwards. The patient showed facial asymmetry. The right part of her face became collapsed while the left part was obvious swelling with a 6 × 6 cm lump. The
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manifestation was ill-defined, hard and immobile. Other signs included trismus, lower lip numbness, elevated upper left palate, and interlinked upper right palate and nasal cavity. The skin showed no sensory disturbance, no swelling, ulceration or fistula formation.

Review of the family history revealed that the patient’s son showed bilateral facial enlargement at his age of two, but no clear diagnosis was made at that time. He received surgical scraping at the age of five. At the age of eight and ten, new lesions were found in his right mandible angle and mentum respectively, and later he received the second surgical scraping.

The radiographic examination revealed that the patient has lost her right maxilla as well as part of the mandible. The multilocular radiolucent expansile lesions were scattered in the mandible combined with some irregular high density areas. The mandible was asymmetric with abnormal left mandibular angle. Teeth alignment showed abnormality and the second premolar in the left lower jaw was missing. A fresh fracture and several old fixtures could be seen in the right mandible (Figures 1 and 2). Histological examination found some long spindle cells, stromal cells as well as many multinucleated giant cells. Hemosiderin was observed in endothelial cells and some surrounding fibroblasts (Figure 3).

Sequencing of the SH3BP2 gene of the proband and four other family members was performed as described previously [13]. A missense mutation in SH3BP2 was found. A single base G→A transition at cDNA nucleotide 1364 in exon 9 resulted in an arginine to glutamine switch (p. Arg415Gln) (Figure 4). The possibility of SNP was excluded in 50 healthy controls.

Based on the findings of clinical signs, radiographic, histologic and molecular examinations together with the family history, the final diagnosis was established as cherubism. The excision of enlargement in her left maxillary and partial left maxillary was finally performed under general anesthesia.

All the aspects of the study complied with the Declaration of Helsinki, 1995. Written informed consents were obtained from the patient and family members. The study was authorized by Ethic Committee, School of Stomatology, the Fourth Military Medical University, Xi’an, China.

Discussion

Cherubism is characterized by progressive, painless, bilateral enlargement of the mandible.

Figure 1. Radiological findings of the proband: General decrease of bone density within the maxilla and mandible compared with other bones (A). Fibrosiscalcification and atrophy can be found in left lung. No substantive lesions are recognized in right lung (B).
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Figure 2. Radiological findings of the proband. A. Panoramic radiograph shows scattered multilocular radiolucent expansile lesions in the mandible combined with some irregular high density areas, a fracture and old fixtures in right mandible. (B–D) CT scanning images of the proband’s head. Maxillary expansion pushes the orbital base upward and causes upturned eyes (B), producing the characteristic “eyes raised to heaven”. The right side of the maxilla (C) and part of the mandible's sclerotin (D) were missing.

and/or maxilla resulting from replacement of bone with multilocular cysts composed of fibrotic stromal cells and osteoclast-like cells. Cherubism should be differentiated from central giant cell granuloma (CGCG), multiple giant-cell lesion syndrome, fibrous dysplasia, brown tumours and Ramon syndrome, which exhibits similar clinical manifestations. CGCG is a rare benign lesion leading to facial deformity and displacement of the teeth, and that lesions usually occur in the mandible and maxilla. CGCG is relatively prevalent in children and young adults, with a higher frequency in females. It can be differentiated from cherubism through histological features. The major lesion of CGCG is unilocular, whereas the lesions of cherubism are usually multilocular [14]. Cone beam computed tomography (CBCT) with low radiation doses can be used to detect small lesions that reveal no obvious enlargement of the face [15]. Pinheiro et al. reported two cases diagnosed as central giant cell lesions and cherubism using CBCT [16]. Multiple giant-cell lesion syndrome is a rare condition with similar clinical manifestations to cherubism [17]. It is characterized by developmental delay, short stature, pulmonary stenosis, and giant-cell lesions of bones and soft tissues. People with mild multiple giant-cell lesion syndrome can be misdiagnosed with cherubism because the giant-cell lesions are frequently found in the jaws [18]. Fibrous dysplasia of the jaw is characterized by benign giant-cell lesions localized asymmetrically in the maxilla rather than the
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Figure 3. H&E staining of the surgical removal samples. Long spindle tumor cells in the left maxillary, calcification (A), fibroblasts (B and C) and multinucleated giant cells (arrows in F) are partially visible. Many tissues have visible bleeding phenomenon (D and E) and hemosiderin (arrows in C) can be observed.

Figure 4. Sequence analysis of SH3BP2 gene in the patient. A. Normal control sequence of exon 9. B. Pedigree. C. Mutation with G→A transition at cDNA nucleotide 1364 in exon 9 of the proband. D. Mutation with G→A transition at cDNA nucleotide 1364 in exon 9 of the proband’s son.
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Table 1. Modified clinical classification for cherubism (Raposo-Amaral et al., 2007, Pérez-Sayáns et al., 2013)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Existence of the mutation without expression of the disease.</td>
</tr>
<tr>
<td>I</td>
<td>Lesion of the mandible without signs of root resorption</td>
</tr>
<tr>
<td>II</td>
<td>Lesions involving the mandible and maxilla without signs of root resorption</td>
</tr>
<tr>
<td>III</td>
<td>Aggressive lesion of the mandible with signs of root resorption</td>
</tr>
<tr>
<td>IV</td>
<td>Lesions involving the mandible and maxilla with signs of root resorption</td>
</tr>
<tr>
<td>V</td>
<td>The rare, massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla and mandible</td>
</tr>
<tr>
<td>VI</td>
<td>The rare, massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla, mandible, and orbits</td>
</tr>
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mandible. The condition usually presents in childhood and is progressive until adolescence [19]. Cherubism can be distinguished from fibrous dysplasia according to the clinical manifestations. Brown tumors are rare benign giant-cell lesions that arise as a result of parathyroid hormone effects on bone tissue in persons with hyperparathyroidism. Brown tumors can occur in both the maxilla and mandible [20]. The age of onset is usually in adulthood. Hyperparathyroidism can be distinguished from cherubism based on the results of biochemical examinations, since serum concentrations of calcium, parathyroid hormone, and alkaline phosphatase are elevated in hyperparathyroidism [21]. Cherubism has also been reported in association with Ramon syndrome, neurofibromatosis [22, 23], fragile X syndrome, a single case of coronal and sagittal craniosynostosis, which is likely to be a coincidental association [24].

SH3BP2 is currently recognized as one of the candidate gene markers for cherubism. SH3BP2 consists of an N-terminal pleckstrin homology (PH) domain, a proline-rich (PR) domain and a C-terminal Src-homology 2 domain (SH2). SH3BP2 may bind to cell membrane lipids via its PH domain and to interact with the SH3 domains of binding partners via SH3 binding motives in the proline-rich domain [25].

The SH3BP2 has 13 exons and by now all the reported mutation sites are located in exon 9, within a 6 amino acid interval (RSPPDG) in the proline-rich domain proximal to the SH2 domain of SH3BP2 [26]. Fifteen types of mutations in SH3BP2 have been identified by now [27]. The hot mutation site is proline P (Pro) mutation for leucine L (Leu), arginine R (Arg), histidine H (His) at 418 of exon 9, other mutations include glycine G (Gly) replaced by glutamic acid E (Glu) or arginine R (Arg) at 420, arginine R (Arg) replaced by proline P (Pro) or glutamine Q (Gin) at 415 [28]. Imai Y found a missense mutation in the Pro418 Arg in a sporadic case [13]. Hyckel reported that the missense mutation of Pro418 His in a familial giant jaw disease [28].

SH3BP2 was expressed in osteoblasts from mandible, iliac crest and giant cell tumor [26]. Carvalho reported that mutation located in exon 4 can also lead to cherubism and a mutation in exon 3 can cause severe cherubism [29]. Missense mutation may also occur far away from SH2 and PH structure domain, which might not affect gene function. Amino acid 415-420 may represent a specific structure domain and the mutations in this site change gene function and result in cherubism.

SH3BP2 plays a critical role in bone remodeling. It regulates bone homeostasis by interfering osteoclast functions, as well as, osteoblast differentiation and function. Sh3bp2/−/− mice exhibited increased growth plate thickness, decreased trabecular bone thickness and bone mineral density, and reduced differentiation potential [30].

A somatic mutation in SH3BP2 has been identified in one individual with central giant-cell granuloma [29]. Also the mutations in PTPN11 and SOS1 [31] have been described in both familial and simplex cases of multiple giant-cell lesion syndrome. The above genes might be used as the molecular marker to differentiate cherubism.
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According to the Raposo-Amaral’s cherubism classification (Raposo-Amaral et al., 2007), the pedigree here classified as grade V cherubism, which is a rare condition characterized by massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla and mandible (Table 1). However, the proband has been misdiagnosed for more than forty years and has received surgical treatments repeatedly since the age of fourteen. As for the best timing for surgical treatment, different opinions have been reported by researchers [32]. The operation is generally suggested till puberty. Early surgery may increase the rate of recurrence. Deformity in the jaw has less influences on children’s psychological development and function of language, thus, early surgery is only recommended for children with serious deformity. In our case, both the patient and her son accepted several operations before or around puberty. The lesions recurred after surgical treatments. The misdiagnosis influenced the decisions on the operation time point and surgical methods. Multi-surgical experiences affected the clinical, radiological and histopathological sighs of the patient and his son, which in turn brought great difficulties in the final correct diagnosis, especially in distinguishing cherubism from CGCG of the jaw [9, 26, 33].

Genetic testing allows the genetic diagnosis of vulnerable abilities to inherited diseases. Here the molecular test of SH3BP2 helped us to give an accurate final diagnosis [34-36]. We found that the proband and her son had a missense mutation in exon 9 of SH3BP2 (p. Arg415Gln). Pérez-Sayáns et al. reported two cases of familial cherubism, uncle and nephew, with the variable clinical involvement, and one case of a woman, who transmitted cherubism without suffering the disease in cherubism. Since the possibility of transmission reaches 50%, it is important to develop genetic counseling for both patients and carriers in order to prevent it from affecting the offsprings [37].

Conclusions

Cherubism is an autosomal dominant inherited bone disease. Depending on the scope and severity of the lesion, clinical symptoms may range from no clinically or radiographical detectable features to unshapely deforming mandible or maxilla with respiratory embarrassment, impaired vision and hearing. Cherubism might be caused by the mutations in SH3BP2 gene. Cherubism should be differentiated from multiple giant-cell lesion syndrome, central giant-cell granuloma, fibrous dysplasia, brown tumors and Ramon syndrome. As for suspected cherubism cases with complicated medical history, gene test of SH3BP2 can be combined with radiographic and histological examinations to make the final diagnosis.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Xiaohong Duan, State Key Laboratory of Military Stomatology, Department of Oral Biology, Clinic of Oral Rare Diseases and Genetic Diseases, School of Stomatology, Fourth Military Medical University, 145 West Changle Road, Xi’an 710032, P. R. China. Tel: 86-29-84776169; Fax: 86-29-84776169; E-mail: xhduan@fmmu.edu.cn

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