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Case Report

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

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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 was diagnosed as "giant cell tumor" at the age of fourteen in a local hospital and received mandibular scraping and radiotherapy twice. At the age of thirty, the patient noticed recurrence of swelling in her face. Then, osteotomy of bilateral mandibular, excision of partial maxillary, together with iliac graft was performed on the patient at the age of forty-six. Five years later, another local swelling was found in her left maxilla, which grew slowly but gradually. 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

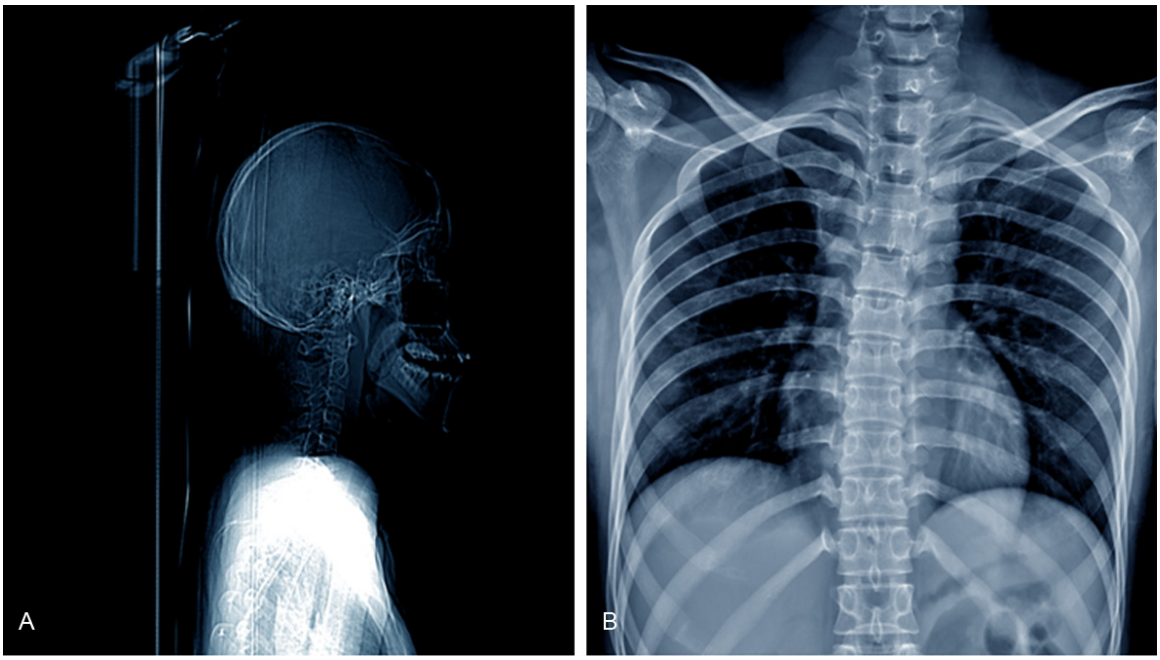

Figure 1. Radiological findings of the proband: General decrease of bone density within the maxilla and mandible compared with other bones (A). Fibrosiscalcification and atrophy can be found in left lung. No substantive lesions are recognized in right lung (B).

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 abnormity 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

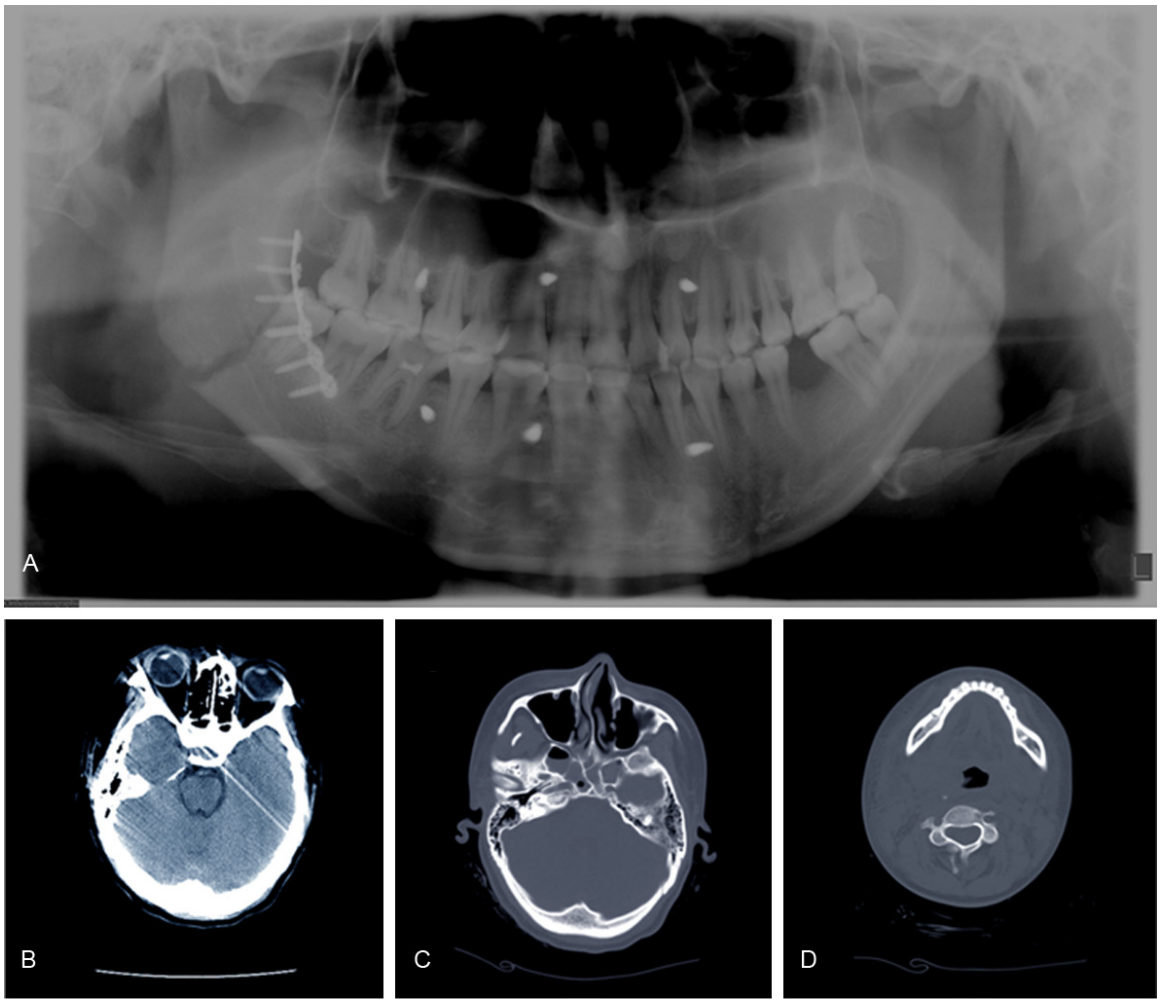

Figure 2. Radiological findings of the proband. A. Panoramic radiograph shows scattered multilocular radiolucent expansile lesions in the mandible combined with some irregular high density areas, a fracture and old fixtures in right mandible. (B~D) CT scanning images of the proband's head. Maxillary expansion pushes the orbital base upwardand 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

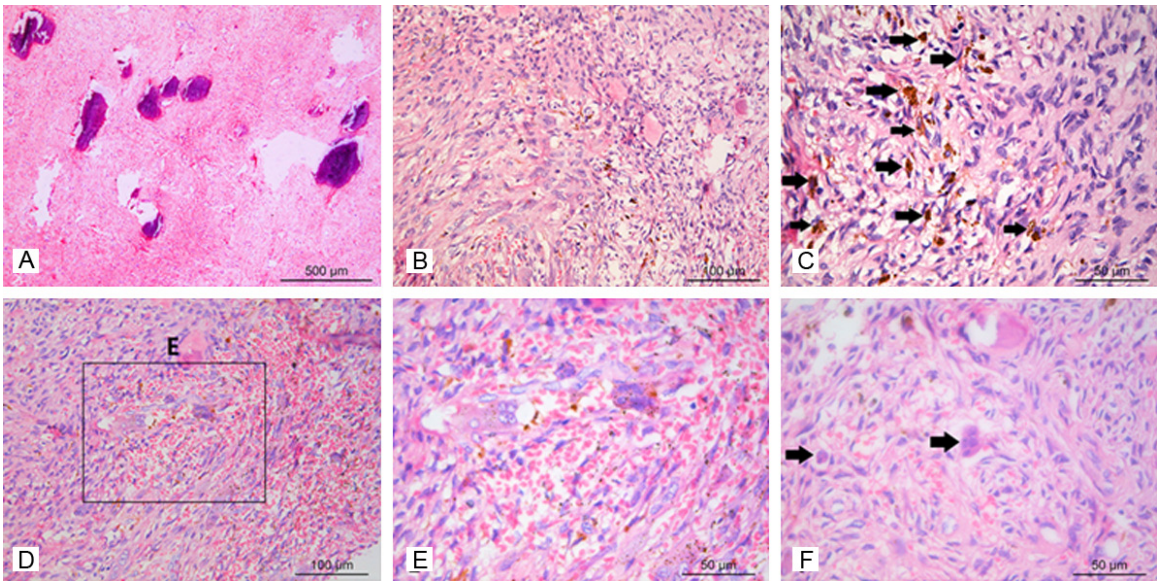

Figure 3. H&E staining of the sugical removal samples. Long spindle tumor cells in the left maxillary, calcification (A), fibroblasts (B and C) and multinucleated giant cells (arrows in F) are partial visible.Many tissues have visible bleeding phenomenon (D and E) and hemosiderin (arrows in C) can be observed.

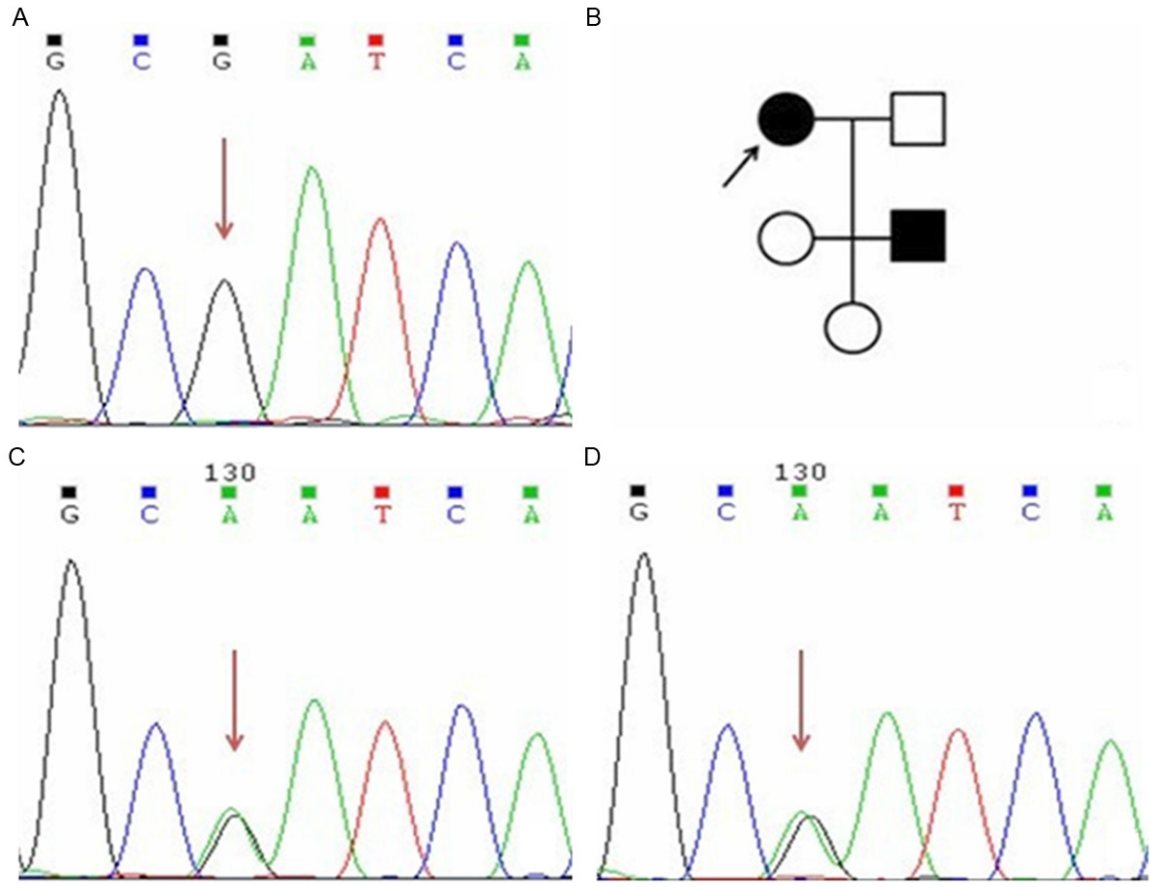

Figure 4. Sequence analysis of *SH3BP2* gene in the patient. A. Normal control sequence of exon 9. B. Pedigree. C. Mutation with G⟶A transition at cDNA nucleotide 1364 in exon 9 of the proband. D. Mutation with G⟶A transition at cDNA nucleotide 1364 in exon 9 of the proband's son.

Table 1. Modified clinical classification for cherubism (Raposo-Amaral et al., 2007, Pérez-Sayáns et al., 2013)

Grade	Definition
0	Existence of the mutation without expression of the disease.
I	Lesion of the mandible without signs of root resorption
II	Lesions involving the mandible and maxilla without signs of root resorption
III	Aggressive lesion of the mandible with signs of root resorption
IV	Lesions involving the mandible and maxilla with signs of root resorption
V	The rare, massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla and mandible
VI	The rare, massively growing, aggressive, and extensively deforming juvenile lesions involving the maxilla, mandible, and orbits

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 interferingosteoclast functions, as well as, osteoblast differentiation and function. *Sh3bp2*$^{KI/KI}$ 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.

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.

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References

[1] Jones WA. Familial multilocular cystic disease of the jaws. Am J Cancer 1933; 17: 946-950.
[2] Lima Gde M, Almeida JD and Cabral LA. Cherubism: clinicoradiographic features and treatment. J Oral Maxillofac Res 2010; 1: e2.
[3] Hyckel P, Berndt A, Schleier P, Clement JH, Beensen V, Peters H and Kosmehl H. Cherubism-new hypotheses on pathogenesis and therapeutic consequences. J Craniomaxillofac Surg 2005; 33: 61-68.
[4] Mani S, Natarajan B, Rajaram K, Sahuthullah YA, Gokulanathan S and Sitra G. Rare form of cherubism: Case report with review of literature. J Pharm Bioallied Sci 2013; 5: S142.
[5] Mehrotra D and Kesarwani A. Cherubism: case report with review of literature. J Oral Maxillofac Surg 2011; 10: 64-70.
[6] Atalar M, Albayrak E, Erdinc P and Bulut S. Cherubism as a rare cause of bilateral expansion of the mandible: radiological manifestations. J HK Coll Radiol 2008; 11: 76-80.
[7] Meng XM, Yu SF and Yu GY. Clinicopathologic study of 24 cases of cherubism. Int J Oral Maxillofac Surg 2005; 34: 350-356.

[8] Özkan Y, Varol A, Turker N, Aksakalli N and Basa S. Clinical and radiological evaluation of cherubism: a sporadic case report and review of the literature. Int J Pediatr Otorhinolaryngol 2003; 67: 1005-1012.
[9] Jain V, Gamanagatti S, Gadodia A, Kataria P and Bhatti S. Non-familial cherubism. Singapore Med J 2007; 48: e253-257.
[10] Roginsky V, Ivanov A, Ovtchinnikov I and Khonsari R. Familial cherubism: the experience of the Moscow Central Institute for Stomatology and Maxillo-Facial Surgery. Int J Oral Maxillofac Sur 2009; 38: 218-223.
[11] Anderson D and McClendon J. Cherubism-hereditary fibrous dysplasia of the jaws. I. Genetic considerations. Oral Surg Oral Med Oral Pathol 1962; 15: 5-16.
[12] Peters WJ. Cherubism: a study of twenty cases from one family. Oral Surg Oral Med Oral Pathol 1979; 47: 307-311.
[13] Imai Y, Kanno K, Moriya T, Kayano S, Seino H, Matsubara Y and Yamada A. A missense mutation in the SH3BP2 gene on chromosome 4p16. 3 found in a case of nonfamilial cherubism. Cleft Palate Craniofac J 2003; 40: 632-638.
[14] de Lange J and van den Akker HP. Clinical and radiological features of central giant-cell lesions of the jaw. Oral Surg Oral Med Oral Pathol; Oral Radiol Endod 2005; 99: 464-470.
[15] Kau CH, Souccar NM, English JD, Kamel SG and Wong ME. The surgical and orthodontic management of cherubism in a growing child. J Craniomaxillofac Surg 2012; 40: 229-233.
[16] Pinheiro LR, Pinheiro JJ, Júnior SA, Guerreiro N and Cavalcanti MG. Clinical and imagiological findings of central giant cell lesion and cherubism. Braz Dent J 2013; 24: 74-79.
[17] Lee J, Tartaglia M, Gelb B, Fridrich K, Sachs S, Stratakis C, Muenke M, Robey P, Collins M and Slavotinek A. Phenotypic and genotypic characterisation of Noonan-like/multiple giant cell lesion syndrome. J Med Genet 2005; 42: e11-e11.
[18] Jafarov T, Ferimazova N and Reichenberger E. Noonan-like syndrome mutations in PTPN11 in patients diagnosed with cherubism. Clin Genet 2005; 68: 190.
[19] Zenn MR and Zuniga J. Treatment of fibrous dysplasia of the mandible with radical excision and immediate reconstruction: case report. J Craniofac Surg 2001; 12: 259-263.
[20] Lessa MM, Sakae FA, Tsuji RK, Araújo Filho BC, Voegels RL and Butugan O. Brown tumor of the facial bones: case report and literature review. ENT: Ear Nose Throat J 2005; 84: 432-4.
[21] Silva E, de Souza P, Barreto D, Dias R and Gomez R. An extreme case of cherubism. British J Oral Maxillofac Surg 2002; 40: 45-48.
[22] Martínez-Tello FJ, Manjón-Luengo P, Martin-Pérez M and Montes-Moreno S. Cherubism associated with neurofibromatosis type 1, and multiple osteolytic lesions of both femurs: a previously undescribed association of findings. Skeletal Radiol 2005; 34: 793-798.
[23] Van Capelle CI, Hogeman PH, van der Sijs-Bos CJ, Heggelman BG, Idowu B, Slootweg PJ, Wittkampf AM and Flanagan AM. Neurofibromatosis presenting with a cherubism phenotype. Eur J Pediatr 2007; 166: 905-909.
[24] Stiller M, Urban M, Golder W, Tiziani V, Reichenberger E, Frege J, Opitz C and Peters H. Craniosynostosis in cherubism. Am J Med Genet 2000; 95: 325-331.
[25] Deckert M and Rottapel R. The adapter 3BP2: how it plugs into leukocyte signaling. Lymphocyte Signal Transduction. Adv Exp Med Biol 2006; 584: 107-114.
[26] Ueki Y, Tiziani V, Santanna C, Fukai N, Maulik C, Garfinkle J, Ninomiya C, doAmaral C, Peters H and Habal M. Mutations in the gene encoding c-Abl-binding protein SH3BP2 cause cherubism. Nat Genet 2001; 28: 125-6.
[27] Reichenberger EJ, Levine MA, Olsen BR, Papadaki ME and Lietman SA. The role of SH3BP2 in the pathophysiology of cherubism. Orphanet J Rare Dis 2012; 7: S5.
[28] Bell SM, Shaw M, Jou Y, Myers RM and Knowles MA. Identification and characterization of the human homologue of SH3BP2, an SH3 binding domain protein within a common region of deletion at 4p16. 3 involved in bladder cancer. Genomics 1997; 44: 163-170.
[29] Carvalho V, Perdigao P, Amaral F, De Souza P, De Marco L and Gomez R. Novel mutations in the SH3BP2 gene associated with sporadic central giant cell lesions and cherubism. Oral Dis 2009; 15: 106-110.
[30] Mukherjee PM, Wang CJ, Chen I, Jafarov T, Olsen BR, Ueki Y and Reichenberger EJ. Cherubism gene Sh3bp2 is important for optimal bone formation, osteoblast differentiation, and function. Am J Orthod Dentofacial Orthop 2010; 138: 140, e141-140, e111.
[31] Hanna N, Parfait B, Talaat I, Vidaud M and Elsedfy H. SOS1: a new player in the Noonan - like/multiple giant cell lesion syndrome. Clin Genet 2009; 75: 568-571.
[32] Hamner JE 3rd and Ketcham AS. Cherubism: an analysis of treatment. Cancer 1969; 23: 1133-1143.
[33] Miah S, Hatani T, Qu X, Yamamura H and Sada K. Point mutations of 3BP2 identified in human-inherited disease cherubism result in the loss of function. Genes Cells 2004; 9: 993-1004.
[34] Holtzman NA, Murphy PD, Watson MS and Barr PA. Predictive genetic testing: from basic re-

search to clinical practice. Science 1997; 278: 602-605.
[35] Davison C, Macintyre S and Smith GD. The potential social impact of predictive genetic testing for susceptibility to common chronic diseases: a review and proposed research agenda. Sociol Health Illn 1994; 16: 340-371.
[36] Collins FS, Green ED, Guttmacher AE and Guyer MS. A vision for the future of genomics research. Nature 2003; 422: 835-847.
[37] Pérez-Sayáns M, Barros-Angueira F, Suárez-Peñaranda JM and García-García A. Variable expressivity familial cherubism: woman transmitting cherubism without suffering the disease. Head Face Med 2013; 9: 33.