Cherubism

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Keywords
SH3BP2 · Autoinflammation · Macrophages · Osteoclasts · Bone destruction

18.1 Case Report

A 21-year-old female visited our hospital with cosmetic concerns regarding her expanded mandible (Fig. 18.1A). Although she had noticed some facial deformity since she was 6 years old, she did not seek medical attention. When she was around 20 years old, she became more concerned about the noticeable gradual expansion of the mandible. There was no family history of enlarged mandibles. Physical examination revealed a bilateral hard bony swelling of the face and a right exophthalmos. There were no signs of pain or paralysis in the orofacial area nor abnormalities in visual field and acuity. Dental examination revealed (i) three missing teeth other than wisdom teeth, (ii) tooth displacement with an impacted right upper canine, and (iii) microdontia with malformed tooth crowns (Fig. 18.1B, C).

A panoramic radiograph (Fig. 18.1D) showed bilateral mandibular expansion with many multilocular radiolucent lesions spreading from the mandibular body to rami on both sides. Obvious radiolucent lesions were also seen in the maxilla. Root resorption of mandibular incisors was noticeable (Fig. 18.1D). There was an impacted tooth in the lower left mental region that appeared to be equivalent to the first premolar. Right first (or second) lower premolar, left lower second molar, and four wisdom teeth were missing. In agreement with these findings, axial computed tomography (CT) images revealed bilateral multilocular and expansile lesions with heterogeneous density destructing the mandible and maxilla. Notably, the bilateral mandibular body and ramus were substantially affected by these lesions (Fig. 18.2A). The right maxillary lesion was significantly larger than the left and progressed into maxillary sinus, orbit, and pterygopalatine fossa (Fig. 18.2B, C). The three-dimensional CT image showed remarkable expansion and disruption of mandibular and maxillary cortical bone as well as an elevated orbital floor on the right side (Fig. 18.2D). Magnetic resonance (MR) imaging was performed to clarify the extent of lesions and to particularly evaluate the orbital involvement

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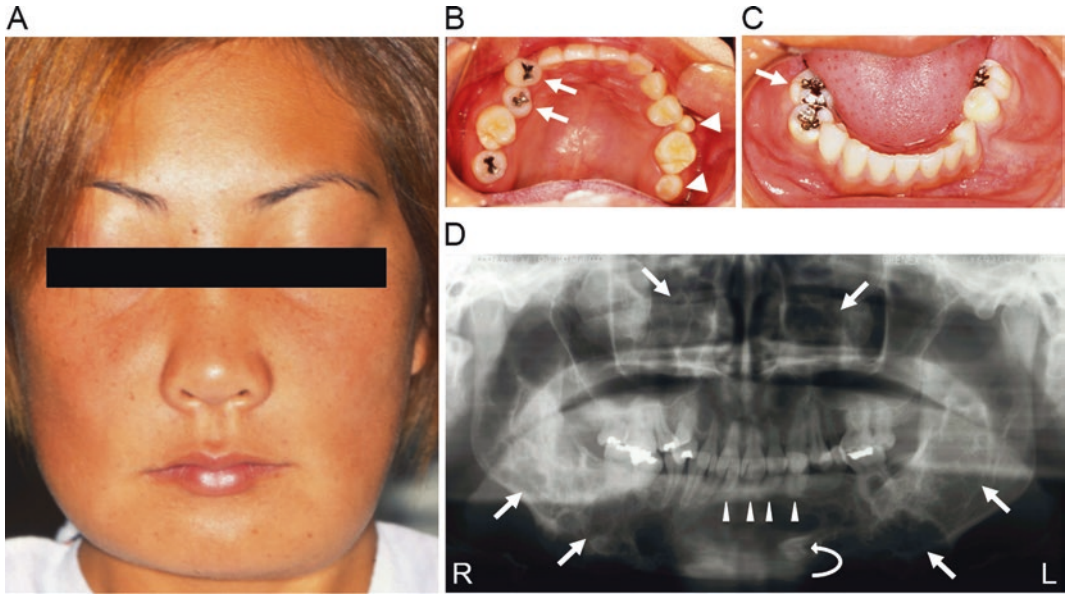

Fig. 18.1 Facial appearance of patient with cherubism (**a**), photograph of oral cavity (**b**, **c**), and panoramic radiograph showing bilateral multilocular radiolucent lesions in the mandible and the maxilla (**d**, arrows). Right upper canine is invisible due to infralabioversion (**b**). Right lower premolar and left lower second molar are missing (**c**). Arrows and arrowheads show displacement of teeth and microdontism with crown malformation, respectively (**b**, **c**). Root resorption of mandibular incisors is noted (**d**, arrowheads). Left lower premolar is impacted (**d**, curved arrow)

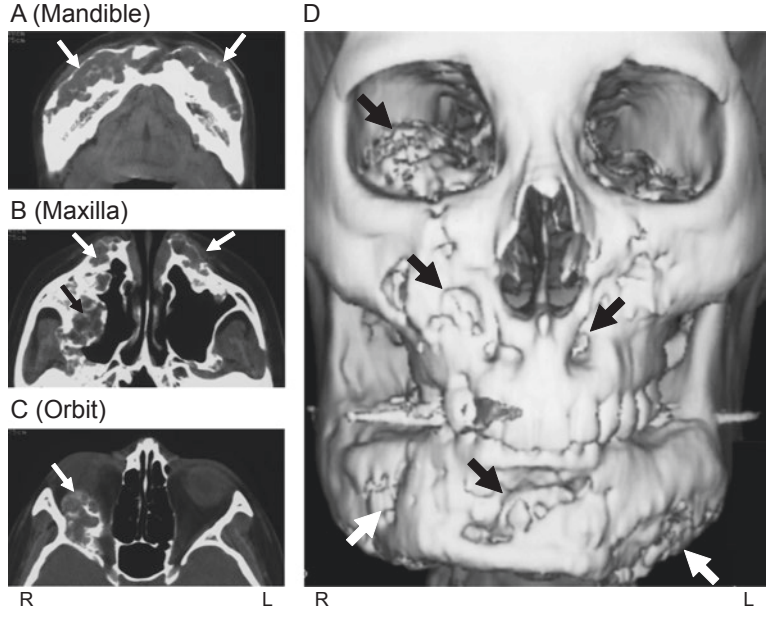

Fig. 18.2 Axial CT images showing multilocular and expansile lesions of the mandible and the maxilla with extension into the right orbit (**a**, **b**, **c**, arrows). Three-dimensional computed tomography image of facial bones of a cherubism patient showing destruction of the mandible and maxilla and elevation of the orbital floor (**d**, arrows). The expansion is more severe in the buccal cortical plates than in the lingual cortical plates. Disruption of the cortex is more severe in the labial side than in the lingual side of the mandible. Coarse bony septa are seen in the mandible, while there is relatively fine trabeculation in the maxilla. D: Courtesy of Dr. Imai (Imai et al. 2003)

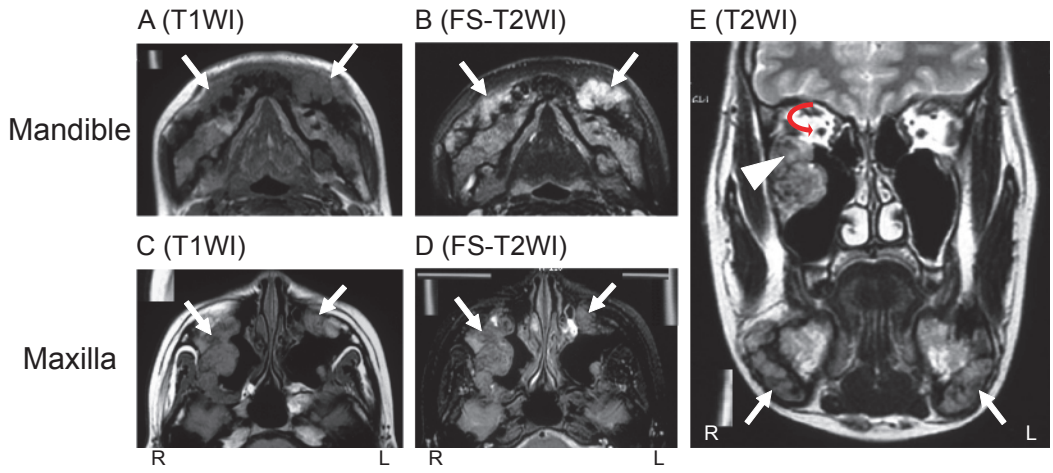

Fig. 18.3 Magnetic resonance imaging detecting lesions (arrows) in both the mandible and maxilla with low-signal intensity on axial T1-weighted images (**a**, **c**: T1WI) and intermediate to high heterogeneous signal intensity on both axial fat-suppressed T2-weighted images (**b**, **d**: FS-T2WI) and a coronal T2-weighted image (**e**: T2WI). The lesion extended into the right orbit (E, arrowhead); however optic nerve is intact on coronal T2WI (curved arrow)

that is likely responsible for the exophthalmos. The mandibular and maxillary lesions showed low-signal intensity on axial T1-weighted MR images (Fig. 18.3A, C) and a heterogeneous intermediate- to high-signal intensity on axial fat-suppressed T2-weighted images (Fig. 18.3B, D). The lesion extended into the right orbit; however, the optic nerve was not damaged on the coronal T2-weighted image (Fig. 18.3E).

A bone scintigram with technetium-99m-labeled methylene diphosphonates (^{99m}Tc-MDP) was performed to investigate skeletal abnormalities beyond the orofacial region. This imaging technique allows for efficient screening of many pathologic conditions due to its high sensitivity. Uptake levels of this radiotracer reflect metabolic and remodeling activity of bone. Results showed increased accumulation of ^{99m}Tc-MDP not only in the mandible and maxilla but also in the right orbital cavity (Fig. 18.4A), while no obvious increased uptake was seen in other regions of the body (Fig. 18.4B). Peripheral blood was sampled for examination of some serum markers for bone turnover. While the level of alkaline phosphatase (ALP) exceeded the reference range (374 IU/L, normal, 112 to 330 IU/L), levels of parathyroid hormone and calcium were within normal limits.

After 2 months of her initial visit, the patient underwent plastic surgery to correct cosmetic deformities by removing bilateral fibrous lesions of the mandible and maxilla. Hematoxylin and eosin (H&E) staining of surgical specimen revealed fibrous stromal tissue that contained a large number of multinucleated giant cells (Fig. 18.5A). The same histological features were observed in specimens of the mandible and maxilla. Malignant characteristics were not seen. These histopathological features were suggestive of giant cell granuloma. Immunohistochemical staining with an antibody against tartrate-resistant acid phosphatase (TRAP), a marker for osteoclasts, showed that the giant cells are strongly positive for TRAP (Fig. 18.5B). Sequencing of genomic DNA from blood cells detected a heterozygous missense mutation in the gene coding for SH3 domain-binding protein 2 (SH3BP2) that causes an amino acid substitution from proline to arginine at amino acid position 418 (Fig. 18.6), confirming cherubism. This non-familial Pro418Arg mutation is most likely a de novo mutation although germline mosaicism cannot be excluded. This patient had no further progression or recurrence of lesions after surgery.

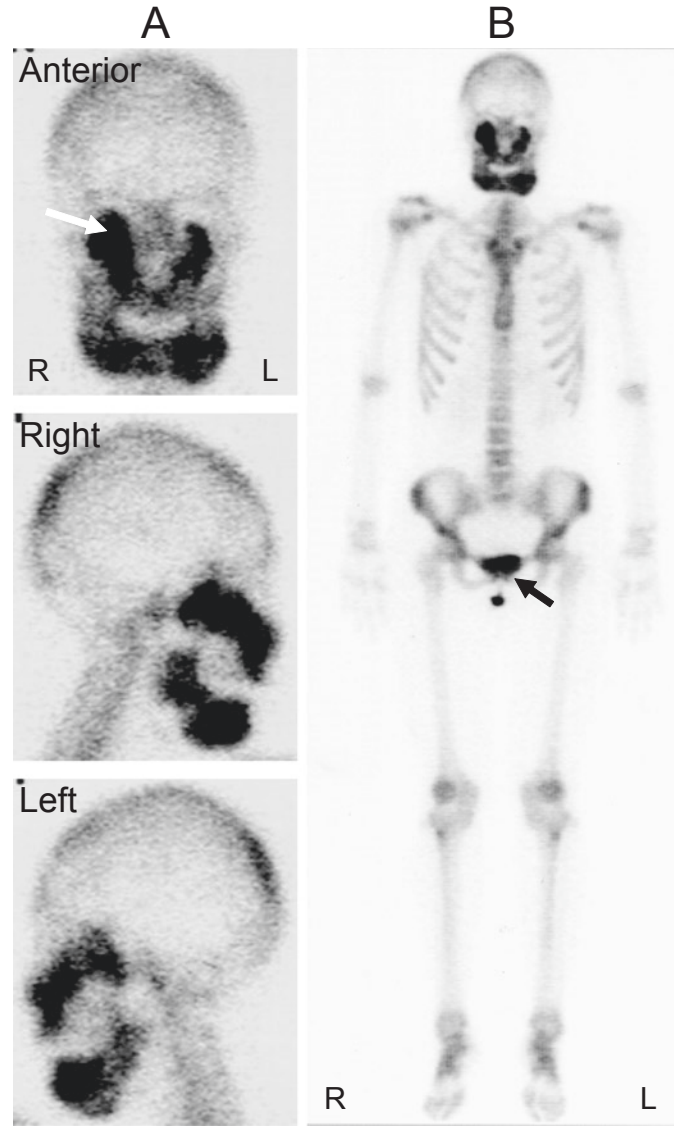

Fig. 18.4 Bone scintigram showing strong radiotracer accumulation in multiple bilateral regions of the mandible and maxilla as well as in the right orbital cavity (**a**, arrow). Anterior whole-body scintigram shows symmetric distribution of radioactivity throughout the skeletal system except the head (**b**). Increased symmetric uptake at the scapulae, clavicles, sternum (angle of Louis), and iliac bones is normal. Increased accumulation in urinary bladder by urine that contains radiotracer is also normal (arrow)

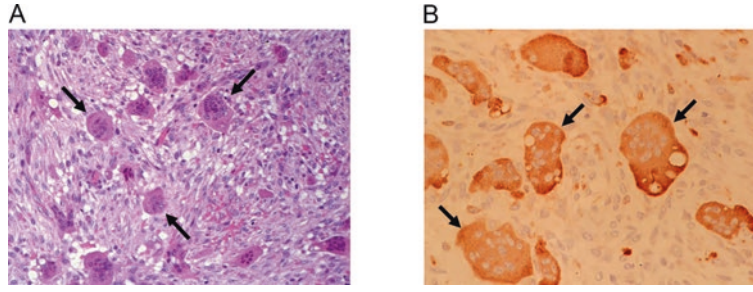

Fig. 18.5 Histological image of surgical specimen demonstrating osteoclast-like multinucleated giant cells within cellular and fibrous tissue (**a**, arrows: H&E staining X100). Immunohistochemical analysis with an anti-TRAP antibody showing TRAP-positive multinucleated giant cells (**b**, arrows: X200). Courtesy of Dr. Imai (Imai et al. 2003)

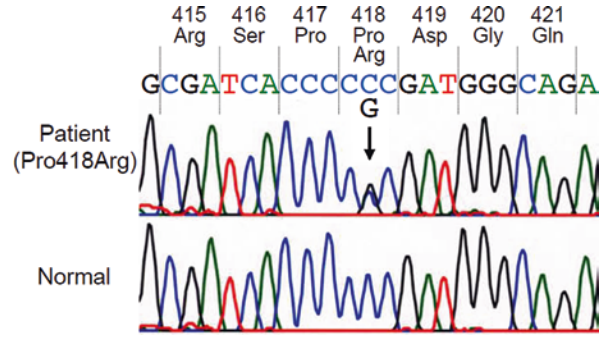

Fig. 18.6 Sequence analysis of the *SH3BP2* gene showing heterozygous Pro418Arg mutation compared to normal sequence

18.2 Diagnosis

The hallmark of cherubism (OMIM#118400) is bilateral symmetrical osteolytic expansion of mandibular and maxillary bone in children that begins around 2–6 years of age. The swelling of the lower face progresses until puberty and often regresses spontaneously thereafter. Typically, X-ray images show multilocular symmetrical cystic changes in the mandible and maxilla. Cherubism usually begins with a swelling of submandibular lymph nodes that may precede and/or exaggerate the enlargement of the lower face, although sometimes this sign goes unnoticed. Cysts most often first develop at the gonial angle of the jaws. The cysts fill with a fibro-osseous tissue mass that can expand significantly, and the bones are further resorbed as the tissue mass expands. This leads to the characteristic facial appearance of full cheeks often accompanied by upward turning of the patient's eyes that are reminiscent of cherubic angels in Renaissance paintings. The upward-turning eyes are caused by invasion of fibrous tissues into the orbital floor. The fibrotic lesions are nonneoplastic. Cherubism is often first diagnosed in children after taking dental radiographs. Progression of lesions varies between cases, even within families, and can be mild. A large number of osteoclastic multinucleated giant cells within fibro-osseous lesions (not adjacent to bone) that have TRAP enzyme activity support the diagnosis of cherubism (Fig. 18.7A). No serological marker for the diagnosis of cherubism has been established.

18.3 Molecular Genetics

Linkage and haplotype analysis for 12 families affected with autosomal dominant cherubism refined the location of the causative gene to a 1.5-megabase-pair (Mbp) interval between genetic markers D4S127 and D4S115 on the short arm of human chromosome 4p16.3 (Ueki et al. 2001). Exon sequencing of candidate genes within the interval detected point mutations in the *SH3BP2* gene of affected individuals in the families. These mutations were not detected in unaffected family members or in 200 healthy controls and cosegregated with cherubism symptoms in all families. All mutations were heterozygous, and the affected amino acids were exclusively located within a six-amino acid sequence (RSPPDG) in exon nine of the *SH3BP2* gene between the SH3-binding domain and SH2 domain of the SH3BP2 protein (Fig. 18.7B). Therefore, mutation analysis of exon nine of the *SH3BP2* gene can be an important tool for confirming the diagnosis of cherubism (Ueki et al. 2001). *SH3BP2* lies within a region that is frequently deleted in individuals with Wolf-Hirschhorn syndrome (WHS; OMIM#194190), but haploinsufficiency of SH3BP2 in individuals with WHS does not result in cherubism or cherubism-like characteristics. This finding and the clustering of amino acid missense mutations in SH3BP2 suggest that the mutations lead to a gain of function (Ueki et al. 2001).

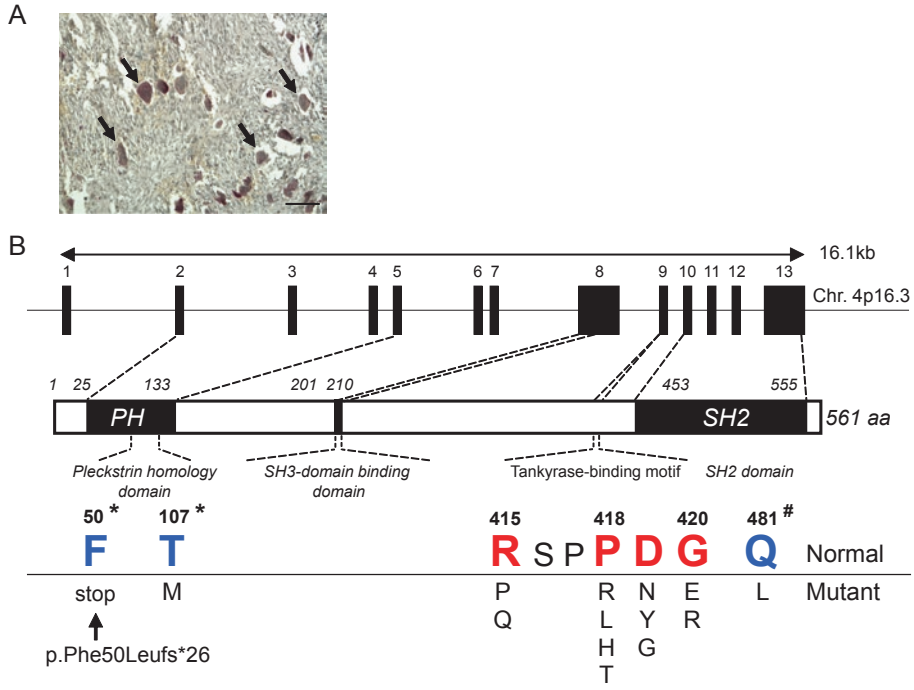

Fig. 18.7 TRAP enzyme activity assay showing TRAP-positive multinucleated osteoclasts in cherubism lesion (**a**, arrows). Gene structure of human SH3BP2 indicating cherubism mutations in SH3BP2 in a six-amino acid interval (415–420) (**b**). Mutations for unusual cherubism cases (*) and for one case of central giant cell granuloma (#) have been reported outside of this region. Modified from Ueki et al. (Ueki et al. 2001). Bar = 100 μm

18.4 Differential Diagnosis

Cherubism cannot be diagnosed by histology alone because histological features of fibrous stromal cells mixed with osteoclastic giant cells are indistinguishable from other giant cell lesion syndromes of bone. Details of histological findings at the various stages of cherubism are rarely described. Differential diagnosis of unusual cases of giant cell lesions, brown tumor of hyperparathyroidism (OMIM#145001), Noonan/multiple giant cell lesion syndrome (OMIM#163950), fibrous dysplasia (OMIM#174800), ossifying fibroma, aneurysmal bone cyst (OMIM#606179), neurofibromatosis type 1 (OMIM#162200), and the hyperparathyroidism-jaw tumor syndrome (HPT-JT) (OMIM#145001) can be challenging. No mutation in *SH3BP2* has been reported in other giant cell lesion syndromes of bone (Reichenberger et al. 2012; Papadaki et al. 2012).

18.5 Molecular Perspectives

SH3BP2 is an adapter protein that plays key roles in the regulation of intracellular signal transduction by coordinating protein–protein or protein–lipid interaction. SH3BP2 was first identified as a protein binding to the SH3 domain of the protein tyrosine kinase c-ABL (Bell et al. 1997). Since then, many binding partners and cell type-specific functions of SH3BP2 have been identified (Reichenberger et al. 2012). Cherubism mutations are located in the RSPPDG hexapeptide region of SH3BP2 between SH3-binding and SH2 domains. The RSPPDG sequence is a consensus motif important for interaction with tankyrase, a member of the poly(ADP-ribose) polymerase (PARP) family that catalyzes post-translational protein modification (Guettler et al. 2011). Tankyrase ADP ribosylates SH3BP2 and regulates SH3BP2 stability through subsequent

SH3BP2 ubiquitylation by ubiquitin ligase RNF146. The ubiquitylated SH3BP2 protein undergoes proteasomal degradation in myeloid cells. Since cherubism mutations uncouple SH3BP2 from tankyrase, the tankyrase-mediated SH3BP2 degradation is inhibited, and mutant SH3BP2 protein is stabilized. This leads to the accumulation of mutant SH3BP2 protein, resulting in elevation of downstream signaling activity in a gain-of-function effect (Levaot et al. 2011).

18.6 Cellular and Biochemical Perspectives

The cherubism knock-in mouse model that harbors a proline to arginine substitution at amino acid position 416 (P416R) of SH3BP2, which is equivalent to the most common P418R mutation in human cherubism patients, replicates many features of cherubism (Ueki et al. 2007). The mouse model shows swelling of the face, mandibular bone erosion, and cervical lymphadenopathy due to postnatal development of inflammatory lesions. This inflammatory lesion develops not only in the face but also in many organs such as the lung, liver, and stomach of the mice. Joint inflammation causes severe erosive bone destruction with increased osteoclast numbers on the bone surface, which is similar to human rheumatoid arthritis. Serum levels of tumor necrosis factor-alpha (TNF-α) are elevated in cherubism mice compared to wild-type control mice. This inflammation is suppressed in cherubism mice lacking TNF-α (Ueki et al. 2007). These phenotypes can be recapitulated in wild-type mice transplanted with fetal liver cells from cherubism mice. Therefore, animal studies suggest that cherubism is an inflammatory bone disease of the face resulting from increased activation of macrophages and osteoclasts and that cherubism is a hematopoietic disorder of myeloid lineage cells. However, while human cherubism mutations are heterozygous (autosomal dominant inheritance), homozygosity is required in mice to achieve a severe cherubism-like phenotype, suggesting that the damaging threshold for SH3BP2 levels in mice may be different from humans. Therefore, most pathological and translational studies in cherubism have been conducted in homozygous mutant mice where the phenotype is strongly expressed.

18.6.1 Pathological Role of Mutant SH3BP2 in Macrophages

Macrophages are cells that phagocytose foreign bodies including bacteria and play an important role in inflammatory regulation and fibrosis through functional changes (Wynn and Vannella 2016). Recognition of microbial components mainly occurs via toll-like receptors (TLRs) on cell membranes of immune cells. Thus, TLRs play a key role in host defense against pathogenic microorganisms that produce pathogen-associated molecular patterns (PAMPs) such as lipopeptides of Gram-positive bacteria and LPS of Gram-negative bacteria. They also recognize cellular debris released from injured or necrotic tissues that is called damage-associated molecular patterns (DAMPs). Bone marrow-derived M-CSF-dependent macrophages (BMMs) from cherubism mice are highly responsive to the ligands that stimulate TLRs by producing increased amounts of TNF-α (Yoshitaka et al. 2014b).

Myeloid differentiation primary response 88 (MYD88) is an essential signal transducer of TLR2 and TLR4, the receptor for lipopeptides and LPS, respectively. It was found that cherubism mice deficient in MYD88 do not develop inflammation responsible for swelling in the face (Yoshitaka et al. 2014b) (Fig. 18.8). Consistent with these findings, cherubism mice crossed with TLR2 and TLR4 knockout mice were rescued from development of inflammation in the face (Fig. 18.8). It was also shown that cherubism inflammation developed even in a germ-free environment (Fig. 18.8), suggesting that DAMPs are sufficient to cause cherubism. Furthermore, elevated levels of mutant SH3BP2 protein enhance the downstream NF-κB signaling pathway through spleen tyrosine kinase (SYK) in macrophages stimulated by TLR ligands, leading to increased TNF-α levels in

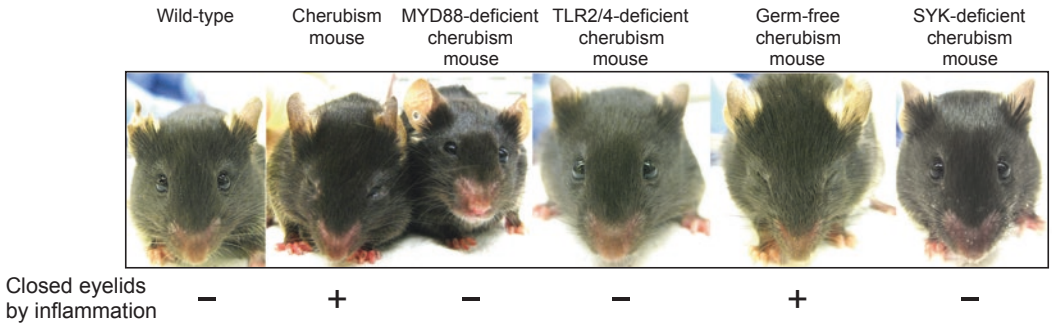

Fig. 18.8 Facial appearance of wild-type and homozygous cherubism mice that develop closed eyelids due to facial swelling from inflammation. Note that eyelid closure in cherubism mice disappears in MYD88-, TLR2/4-, and myeloid cell-selective SYK-deficient cherubism mice, but not in germ-free cherubism mice. Modified from Yoshitaka et al. (Yoshitaka et al. 2014b)

serum responsible for systemic inflammation in cherubism mice (Yoshitaka et al. 2014b). In addition, inflammation in cherubism mice had been shown to occur even in the absence of T- and B-lymphocytes that are important for the adaptive immune system (Ueki et al. 2007). Based on these results, it was concluded that hyperactivation of the TLR-mediated signaling pathway in macrophages by mutant SH3BP2 is responsible for the inflammation in cherubism mice. Thus, cherubism belongs to the spectrum of autoinflammatory disorders and should also be considered a homeostatic inflammatory disease due to the chronic inflammatory reaction against DAMPs (Yoshitaka et al. 2014b). The fibrotic phenotype of human cherubism lesions may be due to impaired regulation of extracellular matrix synthesis mediated by inflammatory macrophages carrying the SH3BP2 mutation.

18.6.2 Pathological Role of Mutant SH3BP2 in Osteoclasts

Osteoclasts are multinucleated giant cells that resorb organic and inorganic mineral components of bone. Like macrophages, osteoclasts originate from the myeloid cell lineage of hematopoietic cells. Receptor activator of nuclear factor kappa-B ligand (RANKL) is a key cytokine that is needed to induce osteoclast differentiation. BMMs from cherubism mutant mice show increased responsiveness to the stimulation with RANKL, resulting in the formation of hyperactive osteoclasts using a mechanism that enhances the induction of nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1 (NFATc1), a master transcription factor of osteoclastogenesis (Ueki et al. 2007; Aliprantis et al. 2008). BMMs expressing mutant SH3BP2 also show an increased responsiveness to TNF-α and can differentiate into osteoclasts with TNF-α alone, without the need for RANKL stimulation. This increased sensitivity to stimulatory cytokines is attributed to increased amounts of SH3BP2 in the cells. Therefore, it was concluded that SH2BP2 is an important regulator of osteoclast differentiation and that mutant SH3BP2 causes inflammatory jawbone destruction via elevated bone-resorbing capacity of osteoclasts in cherubism.

From animal studies, it is concluded that the increased inflammatory response of macrophages is likely responsible for the development of fibrotic lesions in cherubism patients and the cause for lower facial swelling and enlargement of submandibular lymph nodes. Jawbone destruction in cherubism patients is therefore likely attributable to the increased sensitivity of osteoclast precursors to low amounts of cytokines that leads to the formation of osteoclasts with high capacity of bone resorption (Fig. 18.9). Studies of cherubism mice further suggest that the presence of large amounts of TLR ligands in the oral cavity, presumably oral bacteria and DAMPs released during the process of jawbone

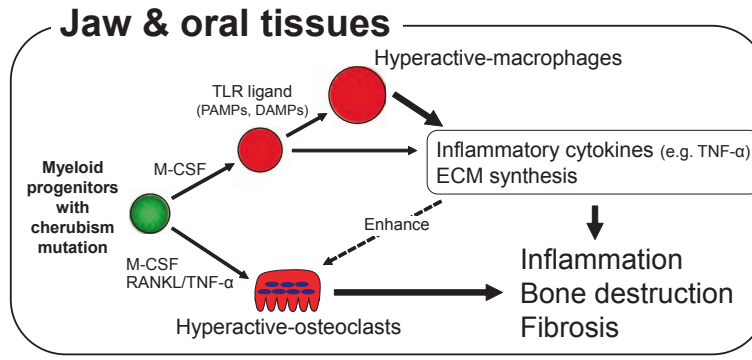

Fig. 18.9 Proposed mechanism for inflammation, bone destruction, and development of fibrous lesion of the jaw in cherubism. ECM, extracellular matrix. Modified from Ueki et al. (Ueki et al. 2007)

remodeling, may contribute to the jaw-specific development of human cherubism lesions. The age-dependent regression of cherubism may be explained with reduced DAMP production in orofacial regions after the cessation of tooth eruption and after the slowdown of jaw remodeling after puberty.

18.7 Therapy and Prevention

Because cherubism is usually self-limiting after puberty, surgical treatment may not be necessary. In most cases, longitudinal observation and follow-up is the initial management. Surgical intervention with curettage, contouring, or resection may be performed for functional, aesthetic, or cosmetic reasons. Surgical procedures are usually performed after the disease becomes quiescent. Aggressive lesions that cause severe functional problems such as airway obstruction justify early surgical intervention (Papadaki et al. 2012). Nonsurgical treatments have been tried in a few instances, but outcomes are not consistent. It is expected that translational studies with mouse models for cherubism may lead to therapeutic options that could either prevent or ameliorate cherubism symptoms.

18.7.1 Calcitonin Administration

Calcitonin is a peptide hormone produced in the thyroid. This hormone is known to inhibit osteoclast function by binding to its cellular receptor. Successful treatment of central giant cell granuloma with calcitonin (Harris 1993) and in vitro inhibition of bone resorption of cells harvested from cherubism lesions with calcitonin (Southgate et al. 1998) suggested effectiveness of calcitonin administration for cherubism treatment. Three cases of cherubism patients treated with calcitonin have been reported. In an 11-year-old boy with rapidly growing lesions in the mandible and maxilla, regression of lesions and restoration of normal contour of the mandible were seen after daily administration of salmon calcitonin by nasal spray for 15 months (De Lange et al. 2007). In a 14-year-old boy who had intraosseous cherubism lesions in the mandible, the lesions regressed after 30 months of salmon calcitonin therapy with nose spray every other day (Etoz et al. 2011). However, a 7-year-old boy with significant mandibular enlargement and facial deformity due to presumed cherubism failed to show clinical or radiological improvement after calcitonin treatment for 6 months (Lannon and Earley 2001). It could be argued that the regression of cherubism lesions after calcitonin treatment may in part be due to the natural course of cherubism. Therefore, further studies are required to assess the efficacy of calcitonin in the treatment of cherubism before it can be used as a general therapy.

18.7.2 Neutralization of TNF-α

Cherubism mice lacking TNF-α do not exhibit inflammation and bone loss (Ueki et al. 2007),

suggesting that TNF-α is a key inflammatory mediator in the cherubism mouse model. Administration of the TNF-α blocker, etanercept, to neonatal cherubism mice prevented the cherubism phenotypes of facial swelling and jawbone destruction (Yoshitaka et al. 2014a). In contrast, administration of the same TNF-α blocker to mice that already had developed cherubism phenotypes failed to improve the inflammation and bone destruction. The results suggest that anti-TNF-α therapy may be effective in young cherubism patients, if treated before the inflammatory phase or bone resorption occurs. Consistent with the results, administration of a TNF-α antagonist adalimumab to two 4-year-old cherubism patients for approximately 2.5 years did not result in lesion regression or prevent lesion expansion in active cherubism. However, histologically the treatment resulted in a significant reduction in the numbers of multinucleated giant cells and TNF-α-positive cells in both cases (Hero et al. 2013). Therefore, early genetic mutation screening in *SH3BP2* followed by early treatment with TNF-α antagonists might prevent or ameliorate the development of cherubism lesions.

18.7.3 Blocking of NFAT Transcription Factors

Tacrolimus (also known as FK-506) is an immunosuppressive drug that is commonly used to lower the risk for organ rejection after transplantation and treatment of various immune diseases. This drug is a calcineurin inhibitor and suppresses immune cell activation and osteoclast formation by inhibiting NFAT-mediated transcriptional activation. Recently, it was reported that tacrolimus enhanced bone formation in a 4-year-old boy with aggressive cherubism by inhibiting osteoclastogenesis and stimulating osteogenesis (Kadlub et al. 2015). After tacrolimus therapy for 1 year, the patient showed significant clinical improvement, including stabilization of jaw size and intraosseous osteogenesis. Immunohistological analysis of granulomatous lesion showed that tacrolimus caused a significant reduction in the number of TRAP-positive osteoclasts and NFATc1 nuclear staining in the cells. Clinical and functional improvement associated with these biological results suggests that blocking of NFAT-mediated transcriptional activation by tacrolimus administration might prevent the need for surgical removal of growing lesions and recurring maxillofacial surgeries in severe cherubism cases, but might not be effective in all patients. Further clinical trials will be necessary to confirm the efficacy and safety of tacrolimus for mild and severe cherubism.

18.7.4 Bone Marrow Transplantation

Because cherubism phenotypes can be transferred through fetal liver cells in mice (Ueki et al. 2007), effectiveness of transplantation of wild-type bone marrow cells to cherubism mice was examined. Transplantation of bone marrow cells from wild-type mice to 6-week-old cherubism mice with developing inflammation as well as to 10-week-old cherubism mice with established inflammation improved facial swelling and jawbone destruction. Elevation of serum TNF-α levels was not detected after wild-type bone marrow transplantation in cherubism mice (Yoshitaka et al. 2015). These studies suggest that bone marrow transplantation might potentially be effective for cherubism patients who are developing cherubism or are already in the active phase.

18.7.5 Inhibition of SYK

Cherubism mice deficient in SYK in myeloid cells do not exhibit inflammation (Fig. 18.8). This result suggests that SYK is a key mediator for macrophage inflammation in cherubism (Yoshitaka et al. 2014b). Several SYK inhibitors have been developed and are currently in clinical trial. Indeed, administration of a novel SYK inhibitor entospletinib improves inflammatory bone destruction in the mouse model of cherubism (Yoshimoto et al. 2018). Effects of SYK inhibitors need to be confirmed by a controlled clinical trial to determine the efficacy and safety in cherubism patients.

In summary, early genetic diagnosis before disease onset will be an important factor for individuals born with cherubism to receive preventive care. It is anticipated that postnatal genetic testing as part of personalized and precision medicine approaches will help to identify SH3BP2 mutations early and that further clinical studies based on translational studies with animal models described here will lead to novel pharmacological therapies that can ameliorate cherubism symptoms or even prevent the development of lesions.

End-of-Chapter Questions

1. When you see an individual who has bilateral jaw swelling that is reminiscent of cherubism, how do you diagnose cherubism histologically and genetically?
2. What will be the difference in treatment strategy between sporadic cherubism patients who already have active lesions and affected newborns with a SH3BP2 mutation born to a cherubism family?
3. Which features in the orofacial region are likely responsible for the jaw-dominant manifestation of cherubism symptoms?
4. How could meticulous oral hygiene potentially impact cherubism?
5. What age-related changes in the orofacial region presumably explain the typical regression of cherubism lesions after puberty?

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