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CASE REPORT

Clinicopathologic and Molecular Characteristics of Familial Cherubism with Associated Odontogenic Tumorous Proliferations

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Abstract Cherubism is a rare autosomal dominant condition affecting the jaws and caused by mutations in the gene encoding for the adapter protein SH3BP2 that maps to chromosome 4p16.3. Cherubism is characterized by symmetrically developing bone lesions in the maxilla and mandible. The lesions have been radiographically and histopathologically well-described. Here, we present a family with cherubism with two of its members featuring odontogenic tumorous proliferations in association with persistent central giant cell lesions (CGCL). Specifically, the proband, a 25-year-old male, developed a radiolucent lesion characterized histologically by central odontogenic fibroma-like proliferation in association with a CGCL component, while his mother, at age 57, was diagnosed with primary intraosseous odontogenic carcinoma with areas of benign fibro-osseous lesions. In both patients the lesions occurred in the anterior mandible and presented with clinical enlargement. The son underwent incisional biopsy and did not have additional treatment. His mother underwent extensive mandibulectomy due to widespread tumor. The son has two affected children with classic cherubism while a third child at age 5, had not shown any features of the disease. Mutation analysis of three affected members resulted in the identification of a heterozygous mutation in *SH3BP2* (c.1244G>C; p.Arg415Pro). To the best of our knowledge, association of cherubism with odontogenic neoplastic lesions has hitherto not been reported in the literature, thus suggesting a relationship between cherubism with disturbed odontogenesis.

Keywords Cherubism · SH3BP2 · Benign giant cell lesion · Odontogenic fibroma · Hybrid COF/CGCL · Odontogenic carcinoma · Intraosseous squamous cell carcinoma · Squamous odontogenic tumor

Introduction

Originally described by Jones et al. [1] as a "familial multilocular cystic disease limited to the jaws", cherubism (OMIM: 118400) represents a rare type of bone dysplasia manifesting, clinically, as asymptomatic, generally bilateral, expansile jaw lesions [1, 2]. The condition starts at 2–5 years of age, continues through puberty and is expected to regress thereafter [3, 4].

Cherubism is autosomal dominant, although several sporadic cases have been described [5, 6]. Penetrance of the disease varies with variable expressivity observed within families [7]. Cherubism is caused by a gain-of-function mutation in the *SH3BP2* gene encoding for the signaling adapter SH3-domain binding protein 2 (SH3BP2) mapped to the chromosomal locus 4p16.3 [8]. To date, 13 different mutations, 12 missense and 1 single-base deletion, have been described, with approximately 80% identified in exon 9 of *SH3BP2* [7, 8].

The phenotypic range of cherubism is broad and expands from subclinical or limited enlargement of the mandible and maxilla to severe overgrowth causing aesthetic, respiratory and speech problems, impaired vision and hearing, as well as dysphagia [9–12]. Reactive cervical and submandibular lymphadenopathy is frequently

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present and may precede the development of intraosseous lesions [9, 13]. Radiographically, cherubism is characterized by diffuse, bilateral, multilocular radiolucencies with few irregular bony septa that affect primarily the mandible but also the maxilla [9, 14, 15].

Histopathologically, cherubism is characterized by multinucleated giant cell-rich fibroblastic proliferation similar to isolated giant cell granulomas [16]. Giant cells in cherubism express markers of osteoclastic origin, while in some cases, eosinophilic, cuff-like deposits surrounding small blood vessels of the stroma can be seen [16].

Rare cases of central giant cell lesions (CGCL) with an associated odontogenic component, predominantly central odontogenic fibroma or central odontogenic fibroma-like (COF), have been previously reported [17, 18]. Tosios et al. [17] have reported on the association of cherubism with a central odontogenic fibroma-like proliferation. The affected mother of the patient described by Tosios and colleagues developed an intraosseous odontogenic carcinoma in association with benign fibro-osseous lesion of the mandible. This family is the topic of the current paper.

Materials and Methods

The proband of the study was a 25-year-old male (Fig. 1, III2) who presented clinically with a mandibular overgrowth. The pedigree of the family consisted of 4 generations affected with cherubism (Fig. 1). Proband and affected family members (II3 and IV1, IV2), besides clinical extraoral and intraoral examination were evaluated radiographically and histopathologically. Gene mutation analysis was performed for three affected members (II3, III2, IV1).

Mutation Analysis for SH3BP2

The mutation analysis protocol was approved by the Institutional Review Board of the University of Connecticut (IRB #07-008) and informed written consent was obtained from the participating subjects. For identification of the causing mutation, approximately 10 mL of peripheral blood were collected from 3 affected individuals (II3, III2, IV1). Genomic DNA was extracted from the samples using a DNeasy Blood and Tissue Kit (Qiagen, Santa Clara, CA, USA). Exon 9 of *SH3BP2* was amplified from genomic DNA by Polymerase Chain Reaction (PCR) using primers designed with Primer 3 (http://primer3.sourceforge.net). Amplifications were performed with primers 5′-CTTGCC GTCCTCACACAGAG-3′ and 5′-TTAGGAACTGTGGAG TCCTG-3′ and sequenced on an ABI PRISM 3730 automated sequencer (Genewiz, South Plainfield, NJ). Resulting sequences were compared to Genebank reference sequence NM_001145856.1.

Results

Clinico-Pathologic Characteristics

The proband (III2), a Caucasian male, presented in 1997 at age 25, with multiple, large and diffuse multilocular radiolucencies occupying the body and the ramus of the mandible bilaterally (Fig. 2). Expansion was observed anteriorly, along with displacement of the roots of involved first right and left mandibular premolars (teeth #21 and #28). Thinning of cortical bone was also noticed. In addition, separate bilateral radiolucent lesions were observed in the maxilla.

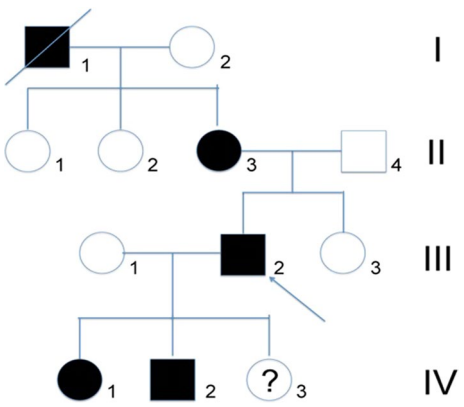

Fig. 1 The pedigree of the family with cherubism. The *arrow* indicates the proband of the current study

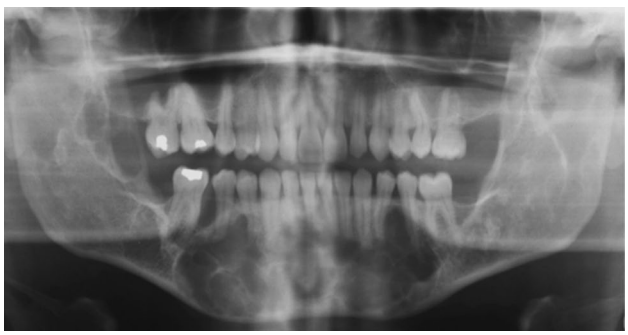

Fig. 2 Panoramic radiograph of the proband (III2) revealing a well-demarcated tumorous growth of the anterior mandible, along with displacement of the roots of involved first right and left mandibular premolars (teeth #21 and #28) and thinning of the cortical bone

An incisional biopsy was performed between second right mandibular premolar and first molar (teeth #29–30).

Gross examination of the biopsied specimen revealed one light tan and four brown soft tissue fragments measuring 2.2×1.2×0.8 cm in aggregate dimension. Microscopically, the lesion featured numerous multinucleated giant cells in a cellular fibroblastic and well vascularized stroma (Fig. 3a, b). Areas of hemorrhage and hemosiderin deposits were evident as were fragments of lamellar bone. The CGCL component was admixed with a COF-like proliferation (Fig. 3c). The latter consisted of islands, cords and nests of bland odontogenic epithelium embedded in dense collagen (Fig. 3d). A diagnosis of hybrid central odontogenic fibroma/central giant cell lesion (COF/CGCL) associated with cherubism was rendered [17]. Within an 18-year follow-up period, the mandibular cherubism lesions of the proband showed no evidence of clinical regression. The patient demonstrated persistent mandibular enlargement with no further changes reported.

The mother of the proband (II3), in 2010 and at age 57, presented with mandibular enlargement characterized by expansile, mixed radiolucent/radiopaque mass extending between first right and left mandibular premolars (teeth #21–28) and associated with numbness of short duration. This enlargement apparently evolved during a 13-year period. Involved teeth presented root displacement along with resorption (Fig. 4). Histopathologically, preparations showed diffusely infiltrating odontogenic neoplasm characterized of irregular islands and cords, as well as round, tadpole in shape, small nests of neoplastic epithelial cells immersed in a fibrous and occasionally sclerotic stroma (Fig. 5a). In areas, the neoplastic epithelial cells showed bland cytologic features and were arranged in a jigsaw puzzle-like architectural pattern reminiscent of squamous odontogenic tumor (SOT) (Fig. 5b). Extensive squamous metaplasia was sometimes present as was dyskeratosis and keratin pearl formation (Fig. 5c). Depending on the area of the tumor examined, lesional cells displayed significant cellular atypia with variation in nuclear size and shape (Fig. 5d). Focally, neoplastic cells exhibited faintly granular to clear cytoplasm and regular appearing mitoses, while scattered atypical mitotic figures were also identified (Fig. 5e). Cystic degeneration was encountered in a few odontogenic islands (Fig. 5f). At the periphery of the lesion, lobular aggregates of multinucleated giant cells and fibroblasts were present within a hemorrhagic background (Fig. 6a, b). Decalcified preparations revealed round to ovoid, basophilic, hypocellular, cementum-like structures or woven bone, in proximity to the epithelial component (Fig. 6c, d). Furthermore, perforation of the cortical bone,

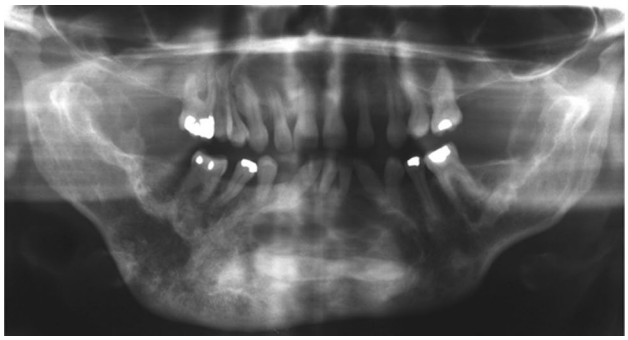

Fig. 4 Panoramic radiograph of the mother of the proband (II3) showing an ill-defined, expansile, mixed radiolucent/radiopaque mass extending between first right and left mandibular premolars (teeth #21–28)

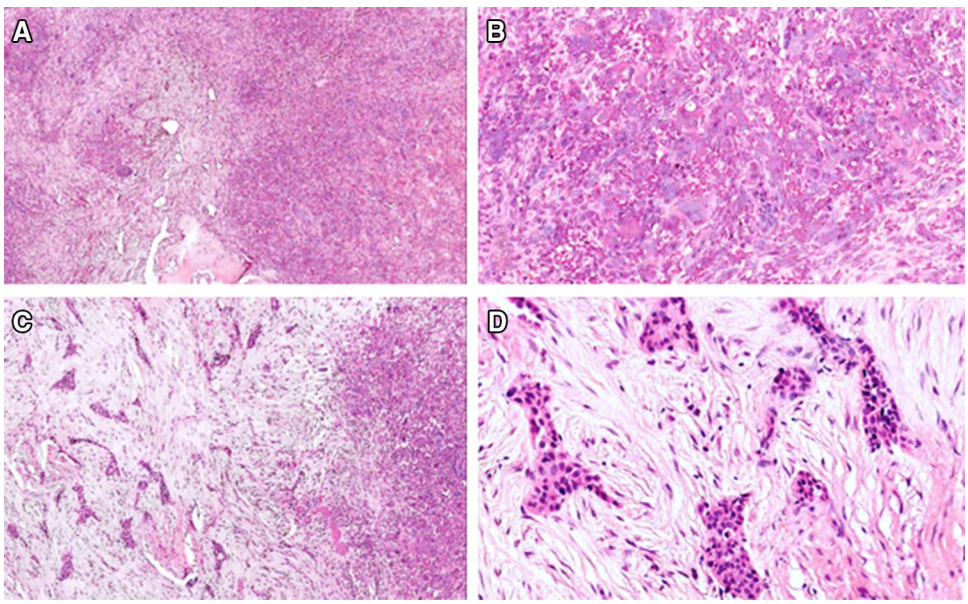

Fig. 3 Histopathologic features of the mandibular tumor of the proband. **a, b** Low- and high-magnification photomicrograph displaying a central giant cell lesion (CGCL) comprised of aggregates of numerous multinucleated giant cells in a cellular fibroblastic and hemorrhagic stroma. **c, d** The CGCL was admixed with a central odontogenic fibroma-like proliferation (COF) consisting of islands, cords and nests of bland odontogenic epithelium embedded in dense collagen (H&E; original magnification **a** ×90, **b** ×250, **c** ×100, **d** ×350)

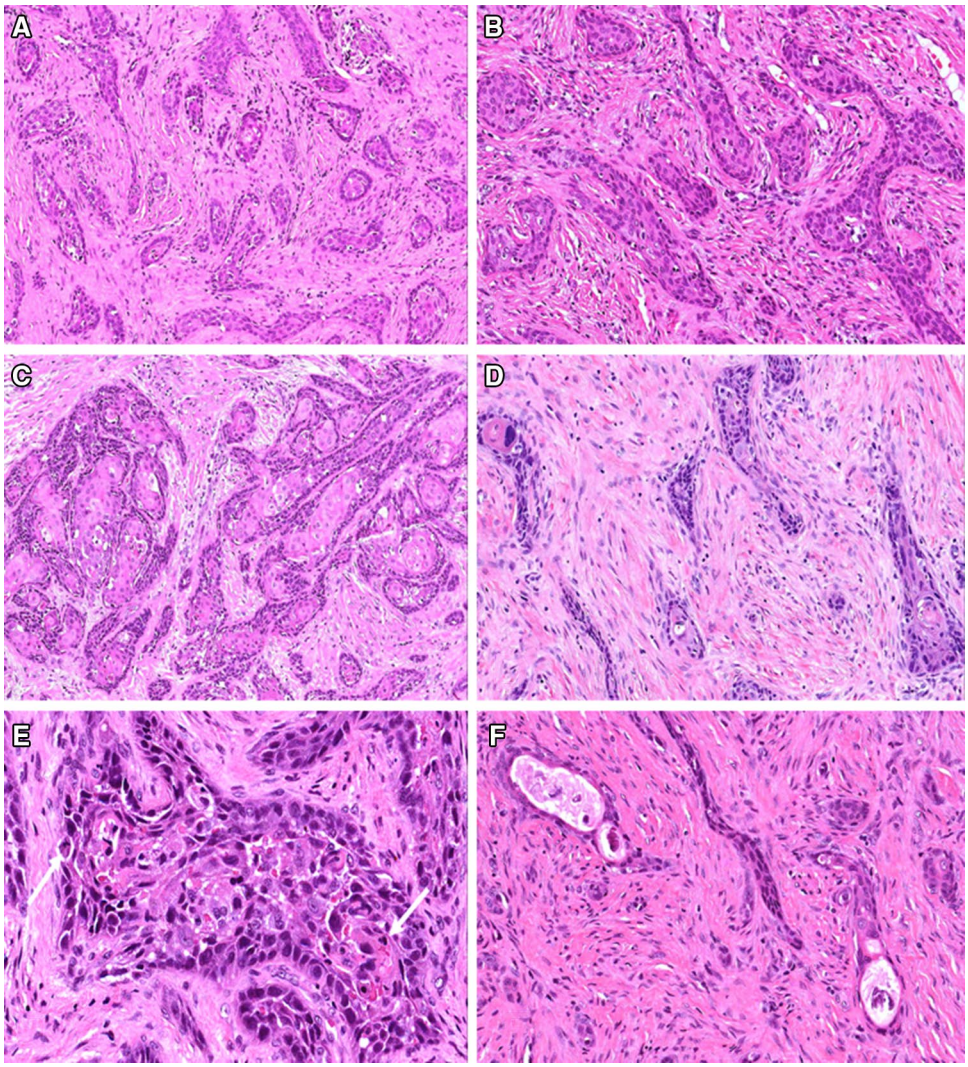

Fig. 5 Microscopic features of the mandibular tumor of the mother of the proband. **a** Histopathologic preparations disclosed a diffusely infiltrating odontogenic neoplasm characterized of irregular islands, cords and nests of epithelial cells embedded in a dense fibrous connective tissue stroma. **b** Squamous odontogenic tumor (SOT) or SOT-like areas composed of cells with bland cytologic features arranged in a jigsaw puzzle-like architectural pattern. **c** Prominent squamous differentiation was present. **d** Some lesional cells displayed significant cellular atypia with variation in nuclear size and shape. **e** Cellular atypia, pleomorphism and scattered atypical mitoses were observed, as indicated by the *white arrows*. **f** Cystic degeneration was encountered in a few odontogenic islands (H&E; original magnification **a** ×180, **b** ×240, **c** ×150, **d** ×200, **e** ×340, **f** ×320)

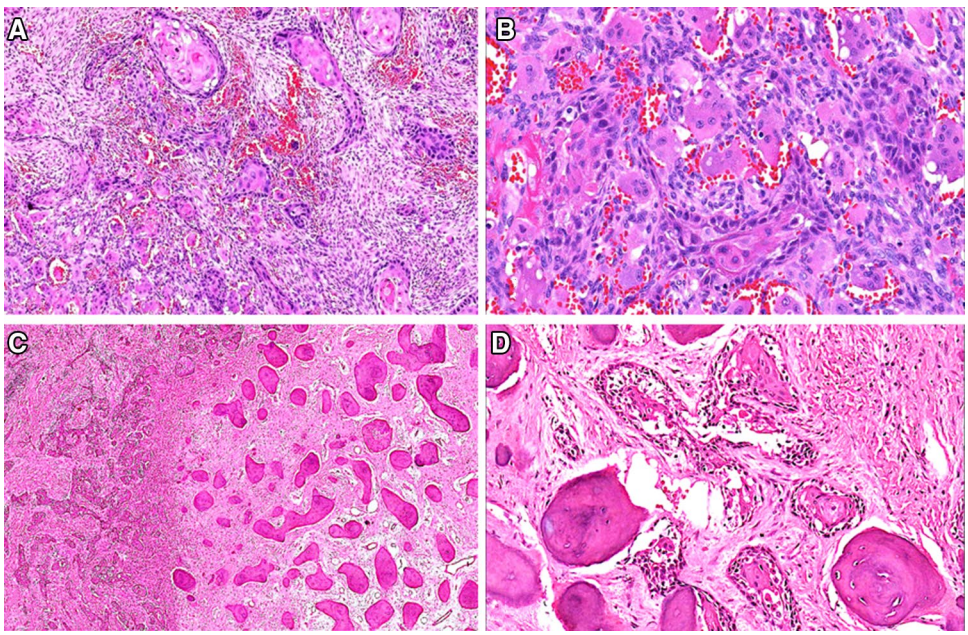

Fig. 6 **a, b** Infiltrating cords, islands and nests of squamous cell carcinoma (SCC) intermingling with aggregations of multinucleated giant cells within a hemorrhagic, dense, fibrous connective tissue stroma. **c, d** Decalcified preparations revealed round to ovoid, basophilic, hypocellular, cementum-like structures or woven bone, juxtaposed to the malignant SCC component (H&E; original magnification **a** ×290, **b** ×340, **c** ×60, **d** ×290)

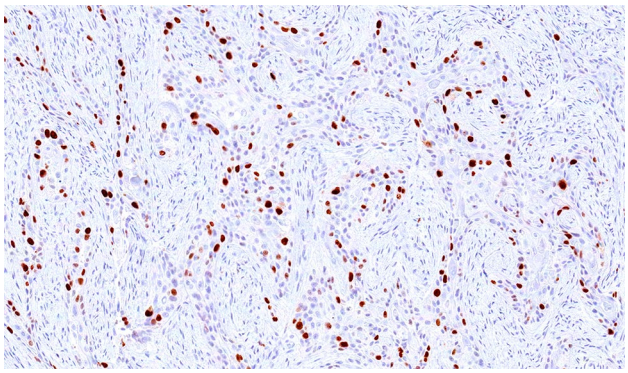

Fig. 7 The Ki-67 proliferation index highlighted approximately 5% of the neoplastic cell population (immunoperoxidase stain; original magnification ×200)

perineural and fat invasion by neoplastic epithelium were encountered.

Immunohistochemical evaluation for Ki-67 (MM1, mouse monoclonal, Novocastra, Buffalo Grove, IL) proliferative index showed nuclear positivity in approximately 5% of epithelial neoplastic cells with more Ki-67 positive cells observed in proximity to associated giant cell aggregates (Fig. 7). Immunostaining against p53 (Bp-53-11, mouse monoclonal, Ventana, Tucson, AZ) was negative throughout the specimen.

Despite the long duration of the lesion and low cell proliferation rate as assessed by Ki-67, the diffusely infiltrative growth pattern of the tumor in combination with the presence of nuclear hyperchromatism and atypia indicated a malignant neoplastic process. Subtyping of the present lesion presented a diagnostic challenge. External consultation was sought and the clinical history, histologic preparations of the specimen and pertinent radiographs were forwarded to three experienced oral pathologists. The following diagnostic interpretations were provided: (1) odontogenic carcinoma, possibly arising in a pre-existing benign odontogenic process, (2) odontogenic carcinoma featuring SOT-like characteristics (carcinoma ex-SOT) and (3) squamous cell carcinoma (SCC) ex-SOT. Based on the clinicopathologic features of the tumor, a final diagnosis of primary intraosseous SCC, probably arising in a pre-existing benign odontogenic lesion (SOT), along with a benign fibro-osseous component, and CGCL (cherubism) was rendered. The patient underwent extensive mandibulectomy with lymph node dissection followed by chemotherapy and subsequent radiation treatment. No evidence of lymph node metastasis was identified at that point, while no recurrences of the primary tumor have been reported within a 6-year follow-up period.

The 6-year-old daughter of the proband (IV1) and her 14-year-old brother (IV2) presented clinically with facial

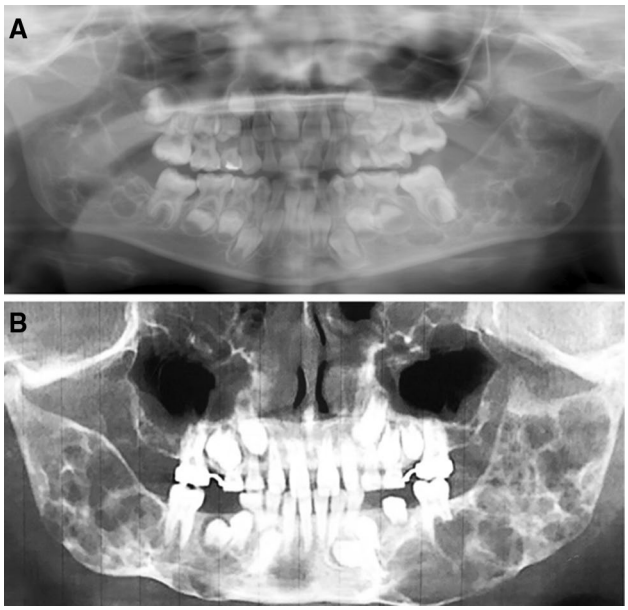

Fig. 8 a, b Panoramic radiographs of the daughter of the proband (IV1) and her brother (IV2) disclosed multiple bilateral radiolucencies affecting the posterior portion and the ramus of the mandible

phenotypic characteristics suggestive of cherubism. Panoramic radiographs disclosed multiple bilateral radiolucencies affecting the posterior portion of the mandible (Fig. 8a, b). Diagnostic biopsies were performed in 2007 and 2013, respectively. Microscopic examination of the submitted specimens revealed identical histopathologic features in both siblings indicative of CGCL. Specifically, numerous aggregates of multinucleated giant cells and spindle-shaped mesenchymal cells were embedded in a highly vascularized and hemorrhagic fibrous connective tissue stroma (Fig. 9a–c). Perivascular eosinophilic fibrin cuffs were also appreciated (Fig. 9d) as were accumulations of hemosiderin within macrophages. To exclude the possibility of a coexistent epithelial component, immunohistochemical staining against pancytokeratin (AE1/AE3, mouse monoclonal, Biocare, Pacheco, CA) was performed. Pancytokeratin was negative in both patients in all examined sections. IV1 and IV2 did not show any evidence of a tumorous growth and close follow-up was recommended at that time.

Molecular Findings

For identification and confirmation of a genetic background, 3 affected individuals (II3, III2 and IV1) underwent *SH3BP2* mutation analysis. All members featured a heterozygous missense c.1244G>C; p.Arg415Pro *SH3BP2* mutation (Fig. 10a–c).

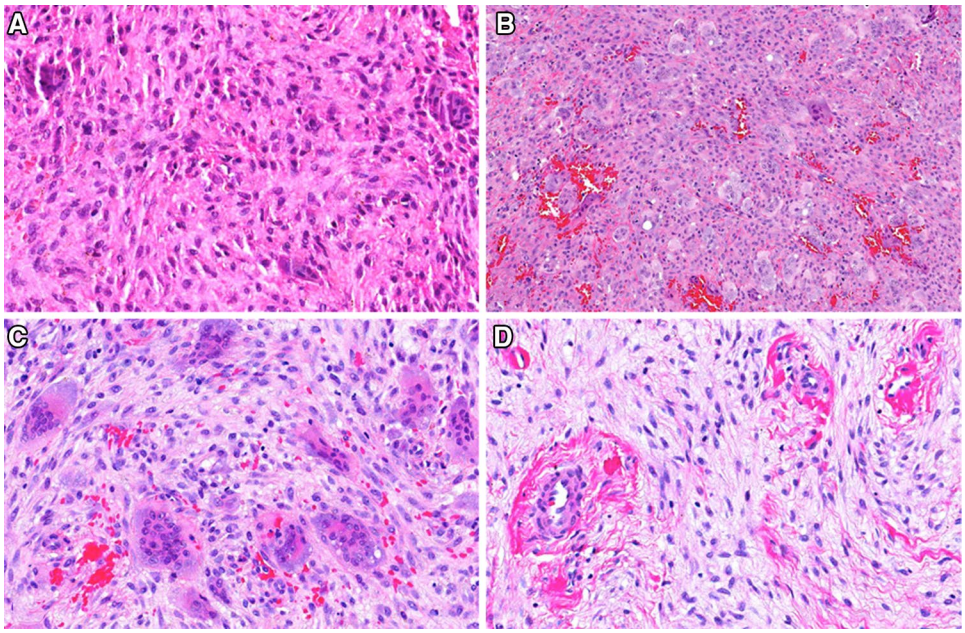

Fig. 9 Histopathologic features of the mandibular radiolucencies of IV1 (**a**) and IV2 (**b**–**d**). Microscopic examination revealed CGCL associated with cherubism in both siblings. **a**–**c** Varying numbers of multinucleated giant cells and spindle-shaped mesenchymal cells were embedded in a highly vascularized and hemorrhagic fibrous stroma. **d** Perivascular eosinophilic fibrin cuffs were appreciated (H&E; original magnification **a** ×320, **b** ×180, **c** ×340, **d** ×340)

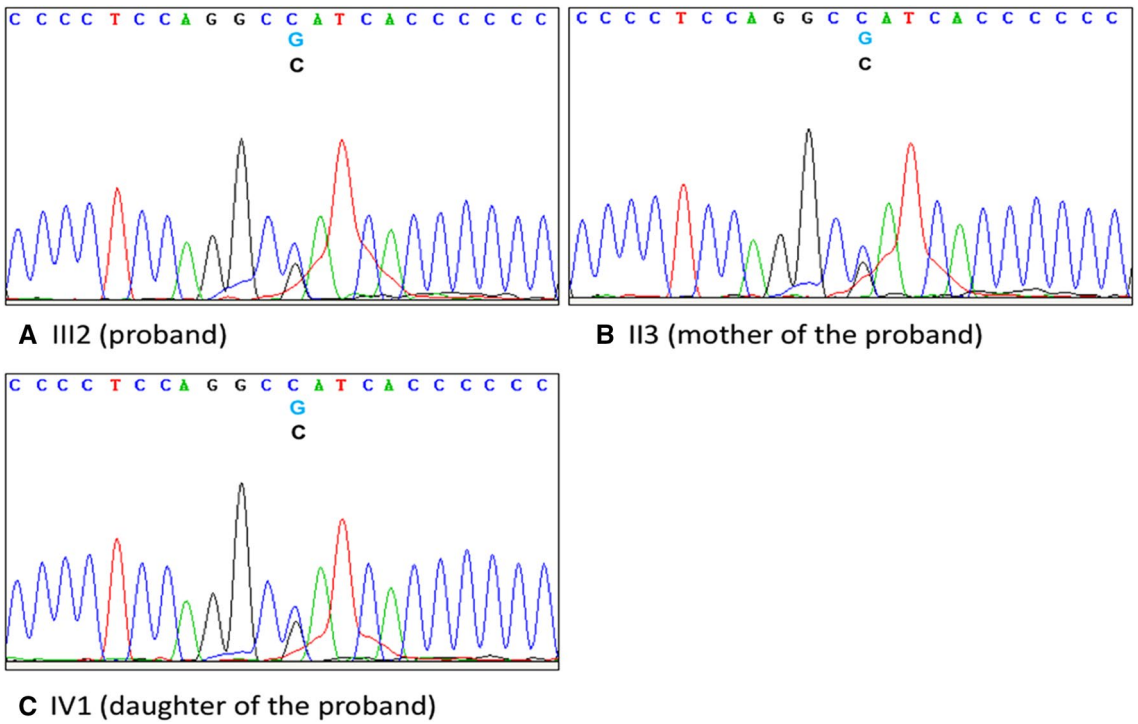

Fig. 10 Sequence chromatograms of III2 (**a**), II3 (**b**) and IV1 (**c**) depicting a heterozygous missense c.1244G>C; p.Arg415Pro *SH3BP2* mutation in all 3 members of the family tested

Discussion

Cherubism is a rare autosomal dominant disorder, which typically appears between the ages of 2 and 7 years [19]. The bilateral, multilocular cystic lesions traditionally affect the posterior portion of the jaws and progress until puberty, when spontaneous clinical regression is usually observed [3, 4, 20]. However, unusual examples of actively expanding lesions beyond puberty, or late reactivation, have been previously reported [21, 22]. In the clinicopathologic study of 24 cases of cherubism by Meng et al. [9], 3/24 (12.5%) patients were older than 21 years during the onset of the

disease. Colombo et al. [23] reported a case of a 27-year-old female with recurrent lesions, exhibiting progressive expansion for 6 years leading to orbital involvement. Lenouvel et al. [22] reported of a 21-year-old female, who, despite a normal clinical course, showed no radiographic regression of the disease after puberty. The quiescent mandibular lesions of the patient demonstrated late reactivation in parallel with the onset of polycystic ovary syndrome. A persistent past-puberty phenotype was also observed in two members of the family reported herein.

Histologically, cherubism cannot be differentiated from CGCL. Of interest in the present pedigree is the association of typical CGCL with odontogenic epithelial tumorous proliferations. The co-existence of a CGCL with odontogenic tumors, although infrequent, has been previously reported. Specifically, the association of CGCL with COF or odontogenic fibroma-like lesions has been well-documented [17, 18, 24–27]. If one perceives such lesions as hybrid COF/CGCL tumors, they account for 13.9% [18] to 21.4% [26] of all COFs and appear to affect females more frequently than males (female:male ratio = 2:1) with a mean age of 31 years at the time of diagnosis [17]. In all aforementioned publications, the CGCL was consistent with central giant cell granuloma, save for a unique case of hybrid COF-like proliferation/cherubism—proband of the current report—included in the clinico-pathologic study by Tosios et al. [17]. Microscopically, the COF and CGCL components can be both distinct and well-separated from each other, or intermingling and traversing [25, 26]. Hyaline globules, peri-epithelial hyalinization, as well as osteoid and woven bone formation within the lesion can be seen [25]. Dysplastic dentin or cystic-like characteristics, however, are absent [17]. Rarely, CGCL have also been identified in proximity to other odontogenic lesions including ameloblastoma [28, 29] and keratocystic odontogenic tumor (KCOT, odontogenic keratocyst) [30], probably representing an epiphenomenon.

Herein, we provide evidence regarding the association of cherubism with a primary intraosseous SCC. The microscopic properties of this lesion were unusual and, although typical morphologic and cytologic features of malignancy were readily appreciated within the tumor, the reported long duration paired with a low cell proliferation rate, as well as the presence of SOT-like areas raised the possibility of a carcinoma ex-SOT. Malignant transformation of SOT appears to be exceedingly rare. Such an example has been previously reported by Ide et al. [31] in a 53-year-old male with a well-defined unilocular radiolucency of the posterior mandible. Microscopically, the tumor showed prominent SOT characteristics along with a few, confined to the peripheral margins, foci of atypical neoplastic cells displaying convincing features of SCC [31]. Locoregional recurrence was observed 2 months after resection of the primary tumor. Notably, the recurrent mass exhibited a combination of moderately differentiated SCC and ameloblastoma-like phenotype [31]. The example of intraosseous SCC ex-SOT presented by Ide et al. [31] and the lesion affecting the mother of the proband (II3) showed certain similarities; both patients were in their 6th decade of life, a benign SOT or SOT-like and a malignant SCC component were identified in both tumors and Ki-67 immunoreactivity, albeit low, was also noticed in both lesions. However, the current case affected the anterior mandible, failed to show any histopathologic features reminiscent of ameloblastic differentiation and demonstrated an apparent CGCL component as part of cherubism.

In addition to the intraosseous SCC, a fibro-osseous proliferation composed of aggregations of hypocellular, cementum-like calcifications or woven bone was identified at the periphery of the malignant tumor. Irié et al. [32] reported a case of sclerosing odontogenic carcinoma with benign fibro-osseous lesion of the mandible in a 67-year-old male patient. Fibro-osseous lesions including fibrous dysplasia and (cemento-) ossifying fibroma have also been associated with aneurysmal bone cyst, simple bone cyst and CGCLs of the jaws [33–35]. Li et al. [36] and Naidu et al. [37] reported on 3 cases of a rare variant of adenomatoid odontogenic tumor encompassed by a prominent reactive cemento-osseous external shell. All 3 cases occurred in the anterior maxilla in patients in the second and third decade of life [36, 37]. Histopathologically, this external shell comprised of woven and lamellar bone trabeculae amalgamated into a solid mass by a thick enveloping coat of cementum [36, 37]. In contrast to these cases, the fibro-osseous lesion associated with the current example of primary intraosseous SCC was more localized and microscopically resembled cemento-ossifying fibroma.

The occurrence of odontogenic tumorous proliferations in two members of the herein presented family with confirmed history of cherubism and persistent mandibular CGCLs is unique and may provide a better understanding regarding the relationship of cherubism with molecular mechanisms underlying odontogenic neoplasia. The tumors affecting the proband and his mother displayed different histopathologic features, however, both lesions were localized in the anterior portion of the mandible with expansion into the premolar area. Notably, these sites are traditionally not affected by cherubism, which favors the posterior mandible and the ramus. The clinical and radiographic similarity of the lesion of the proband to that of his mother has necessitated close follow-up of the proband. Up to now, there is no evidence of new expansion or progression of the lesion.

The reported hybrid COF/CGCL and the primary intraosseous SCC may represent exceedingly rare examples of COF and central SCC colliding with cherubism-related

CGCL. However, we deem that the possibility of development of collision tumors in two patients of the same pedigree with the same underlying condition (cherubism) is even slimmer. Histopathology indicated that in certain areas the CGCL and odontogenic tumorous component were admixed. This observation can support the hypothesis that the CGCL of cherubism induced a COF- and an SOT-like proliferation, which underwent malignant transformation into intraosseous SCC in the latter.

In the current study, we detected a heterozygous missense mutation of *SH3BP2* (c.1244G>C; p.Arg415Pro) in the proband, his mother and daughter. Mutations in cherubism are clustered within a six-amino acid interval (amino acids 415–420, RSPPDG) of the proline-rich domain proximal to the SH2 domain of *SH3BP2* [7, 8]. Mutations in remaining exons are rare. SH3BP2 protein differentially binds to the src homology 3 (SH3) domains of certain signal transduction pathway proteins and appears to induce B cell receptor activation, NK cell mediated cytotoxicity and basophilic cell degranulation [38–41]. Additionally, mutant *SH3BP2* induces upregulation of the transcription factor NFATc1 in RANKL/M-CSF-stimulated osteoclast precursors leading to the formation of excessive numbers of hyperactive osteoclasts [42, 43]. Interestingly, RANKL, its receptor (RANK) and osteoprotegerin (OPG), a decoy receptor for RANKL, appear to participate in the pathogenesis of CGCL [44]. Recent in vivo studies in a mouse cherubism model have demonstrated the role of tumor necrosis factor-alpha (TNF-a) through TLR2/4-MYD88 signaling, indicating that the combination of oral microorganisms with active bone remodeling are responsible for the jaw-specific lesions of the disease [45]. Furthermore, it has been proposed that a mutation in *SH3BP2* may affect factors controlling odontogenesis [46], in particular upregulation of homeobox gene Msx-1 that can trigger proliferation of residual odontogenic epithelium [47]. Hence, an SH3BP2-mediated increase of Msx-1 expression in patients with cherubism could potentially be responsible for activation of odontogenic epithelial rests and the development of neoplastic tumors of odontogenic origin.

In conclusion, we presented the clinicopathologic and molecular characteristics of a unique example of familial cherubism manifesting with associated odontogenic tumorous proliferations in two members who also exhibited a persistent phenotype past puberty. Interactions between the molecular pathways underlying cherubism and odontogenesis such as gain-of-function mutation of *SH3BP2* and possible overexpression of Msx-1 can provide a plausible explanation for this exceedingly rare phenomenon. It would be interesting to study second-hit mutations in this family that might explain this extremely rare phenomenon. Both the daughter of the proband (IV1) and her brother (IV2) showed clinical phenotypic and microscopic signs of cherubism and are being closely monitored for the development of tumorous growths.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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