

CASE REPORT

Ramon's Syndrome: A Rare Entity

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ABSTRACT

Introduction: Ramon et al in 1967 described a condition, which included mental retardation, fibrous dysplasia of the maxilla and stunted growth. De Pino et al described a Brazilian family of four who had the same features as that of Ramon's syndrome in association with juvenile arthritis. Cherubism was first described in 1933 by Jones as 'familial multilocular cystic lesion of the jaws', a rare benign fibro-osseous disease of the jaws, which is transmitted as an autosomal dominant trait. Affected children usually present before five years of age with painless progressive swelling of the cheeks, frequently associated with dental malformations. It progresses until puberty, and shows partial or complete spontaneous involution in adulthood; therefore, management is mostly conservative. The condition was initially characterized as familial, particularly as a form of craniofacial fibrous dysplasia. The children affected with cherubism do not usually show mental or physical deformities, but when cherubism is associated with other syndromes like Noonan-like syndrome, Ramon syndrome, and Fragile X syndrome, mental and physical deformities may be seen.

Case report: This is a case report of a 12-year-old boy who reported with a massive painless bilateral swelling of the face, which has been increasing since the age of 2 years. The patient had multiple unerupted teeth, gingival hyperplasia, hearing loss and mental retardation. A detailed case report, including the histopathology, radiographic features (extraoral, CT and MDCT), and management of the case will be discussed in detail.

Keywords: Cherubism, Ramon's syndrome, Gingival hyperplasia.

INTRODUCTION

Fibro-osseous lesions are diverse processes that cause bone destruction, which is replaced by fibrous tissue containing a newly formed mineralized product.¹ Cherubism is a rare hereditary disorder characterized by a non-neoplastic lesion that causes bilateral bony enlargement of the jaws.² According to the World Health Organization classification, cherubism belongs to a group of non-neoplastic bone lesions that affect only the jaws.³ Bilateral involvement of the mandible is a characteristic feature of cherubism, but one case of unilateral cherubism has also been reported.⁴

CASE REPORT

A 10-year-old male patient reported to Amrita Institute of Medical Sciences, Kochi with a chief complaint of bilateral swelling of the lower jaws, increasing gradually since the age of 2 years. It was not associated with many symptoms except the disfigurement of face. Past medical history revealed that he had epileptic seizures since the age of 7 months, for which he was taking phenobarbitone and valproic acid initially and now has changed to carbamazepine and clobazam. Also, it was reported that there was delay in the milestones of the patient (Figs 1 to 3).



Fig. 1: Appearance on reporting to the department



Fig. 2: Swelling of the mandible



Fig. 3: Dumb-bell shaped appearance



Fig. 4: Teeth embedded in gingiva

On history taking, the parents were 3rd degree consanguinity once removed. The patient had two younger siblings, an 8-year-old female and a 3-year-old male; both of whom did not have any relevant medical history. The clinical and radiographic examination of the parents did not reveal any relevant pathology. No family history of lesions of the jaw or gingiva was reported. The patient was 131 cm in height (less than third percentile) and weighed 30 kg. The head circumference measured 51.5 cm. The patient had a history of mental retardation and suffered from loss of hearing. Brainstem auditory evoked response showed no peaks even at 99 decibel confirming bilateral profound sensory neural hearing loss. The progressive loss of hearing was detected at the age of 6 years. Ophthalmologic examination revealed bilateral partial optic atrophy with pale anomalous disc and areas of retinal pigmentary disturbances. On extraoral examination, bilateral expansion of mandibular angles and ramus was observed. The swelling had gradually increased in size and was not associated with any pain or paresthesia. The lesions were firm to palpation and there was enlargement of the submandibular lymph nodes. The submandibular lymph nodes were hard and mobile on palpation. The swelling of the mandible was larger on the right side in comparison to the left. On the left side, the swelling measured 8 × 8 cm in size supero-inferiorly and 8 cm from the corner of mouth laterally. On right side the swelling was 9 × 9 cm in size supero-inferiorly and laterally expanded 8 cm from the corner of mouth. Both swellings were bony hard in consistency and nontender. The margins of the swellings met at the symphysis region giving a 'dumbbell' like appearance. The skin over the face seemed to be stretched over the swelling but there was no evidence of scar, pigmentation or sinus. The mouth opening was normal. On intraoral examination, the maxillary and mandibular arches were inverted 'V' shaped, narrow and high. There was generalized gingival swelling of all the four quadrants with hypertrophy of both labial and lingual gingiva. The gingiva was pale and fibrotic. The gingival swelling was extensive and covered most of the teeth with only the incisal edges of a few teeth being visible in the oral cavity (Fig. 4).

Blood investigations (serum calcium, phosphorous, alkaline phosphatase) were within the normal ranges.

RADIOGRAPHIC FEATURES

The panoramic view revealed bilaterally expansile, multi-loculated osteolytic lesions involving the entire body as well as the rami of mandible with sparing of condyles. The lesion was associated with marked expansion, and cortical thinning with disappearance of the cortex in certain regions. Posteroanterior view of skull reveals the involvement of posterior maxilla with multilocular radiolucency. Locules appear larger in the right side (Figs 5 and 6).

The MDCT image gives the impression of an expansile lytic lesion with bilateral and symmetric involvement of maxillary and mandibular bones, which were typical of cherubism (Figs 7 to 12).

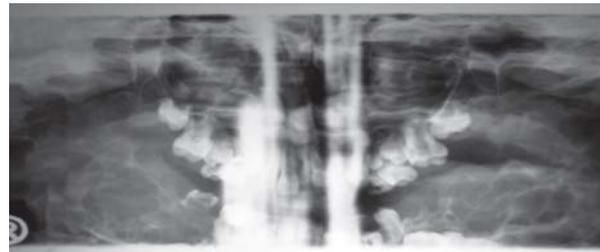


Fig. 5: Orthopantomogram (OPG)



Fig. 6: PA skull

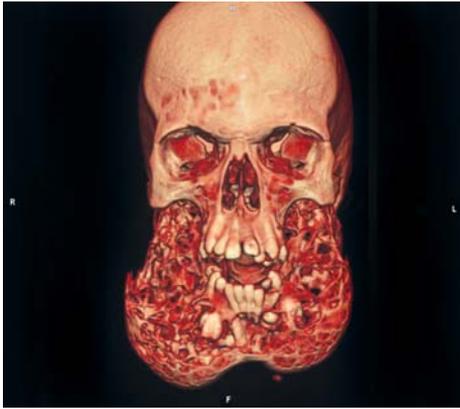


Fig. 7: MDCT



Fig. 11: MDCT mandible—superior view



Fig. 8: MDCT side view

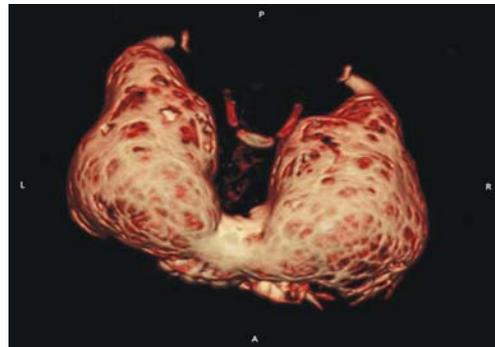


Fig. 12: MDCT mandible—inferior view

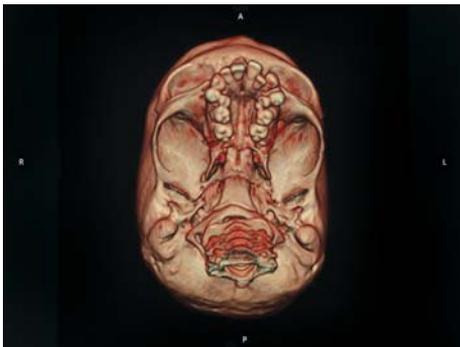


Fig. 9: MDCT base of skull

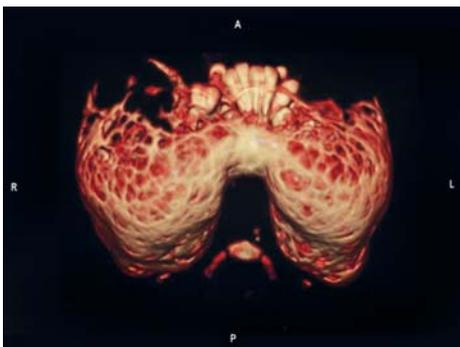


Fig. 10: MDCT mandible

SURGICAL PROCEDURE

Incision biopsy was carried out intraorally under general anesthesia. The biopsy showed bone resorption, and replacement by a cellular connective tissue stroma containing numerous multinucleate giant cells. And under high resolution, delicate connective tissue stroma with numerous fibroblasts, extravasated RBCs and multinucleate giant cells were appreciated. Peripheral eosinophilic cuffing of vessels was also seen, which was suggestive of cherubism (Figs 13 to 16).

Surgical debulking and contouring under general anesthesia was planned upon accordingly. Under standard betadine and towel preparation, visor incision was marked in the upper neck crease for cosmetic purpose. Local anesthetic with vasoconstrictor was injected subcutaneously for hemostasis. Initial incision was placed through skin and subcutaneous tissues to the level of platysma. Skin is retracted and incision deepened through the platysma. Facial vessels were isolated, divided and clamped bilaterally. Dissection through the deep cervical fascia at the level of initial incision and then superiorly to the level of mandibular lower border was done, thereby protecting the marginal mandibular nerve. Subplatysmal flap was raised superiorly up to lower border of mandible, exposing the pathology. Buccal and lingual cortical expansion was noted bilaterally sparing the mandibular symphysis. The involved cortices were thinned/hollowed out with 'honey-comb' appearance, and perforated at many sites. The coronoid

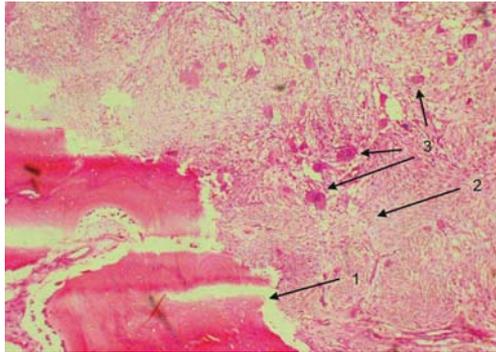


Fig. 13: Low power view showing bone resorption (1) and replacement by a cellular connective tissue stroma (2) containing numerous multinucleate giant cells (3)

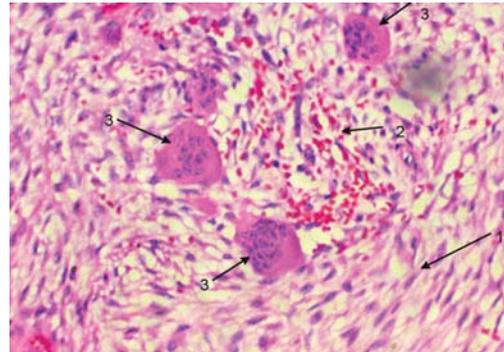


Fig. 15: High power view showing a delicate connective tissue stroma with numerous fibroblasts (1) extravasated RBCs (2) and multinucleate giant cells (3)

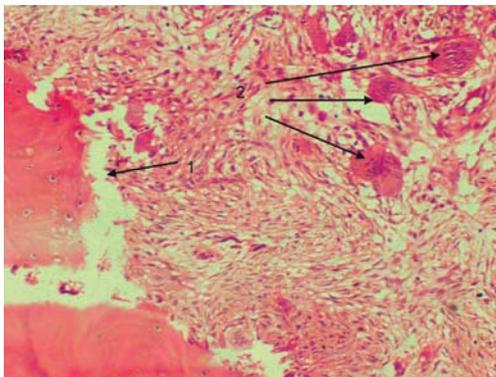


Fig. 14: Higher power view of the previous focus the giant cells (1) and bone resorption (2) being better appreciated

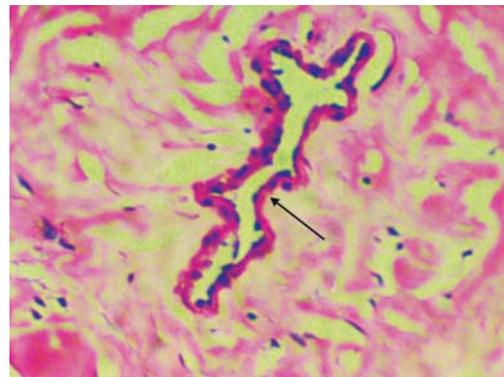


Fig. 16: Perivascular eosinophilic cuffing seen in cases of cherubism

processes were involved in the pathology. Condyles/TM joints were found to be uninvolved. The marrow had white gritty consistency and could be scooped out easily. Debulking of the lesion was carried out preserving the inferior alveolar neurovascular bundles and teeth buds. Bony margins were smoothed, hemostasis achieved and wound closed in layers over suction drains. The patient was followed up for 3 months postoperatively (Figs 17 to 20).

DISCUSSION

Cherubism was first described in 1933 by Jones as 'familial multilocular cystic lesion of the jaws'.⁵ Cherubism is a rare benign fibro-osseous disease of the jaws.⁶ Affected children usually present before five years of age with painless progressive swelling of the cheeks, frequently associated with dental malformations. It progresses until puberty and shows partial or complete spontaneous involution in adulthood; therefore, management is mostly conservative. The condition was initially characterized as familial, particularly as a form of craniofacial fibrous dysplasia.⁷⁻¹⁰ Now, both hereditary and sporadic cases have been reported and recent genetic studies have shown it to be a separate entity at the molecular level.^{11,12} The gene for cherubism has been mapped to seven mutations in the gene



Fig. 17: One month postoperative

encoding SH3-binding protein SH3BP2 on chromosome 4p16.3 that cause cherubism.^{10,11} The children affected with cherubism do not usually show mental or physical deformities, but when cherubism is associated with other syndromes like Noonan-like



Fig. 18: One and a half months postoperative



Fig. 20: Preoperative and postoperative changes



Fig. 19: Two months postoperative

syndrome,^{13,14} Ramon syndrome,¹⁵ fragile X syndrome, mental and physical deformities may be seen.¹⁶ Grading of cherubism based on the location of the jaw lesions have been described by Seward and Hankey¹⁷ as follows:

Grade I: Involvement of bilateral mandibular molar regions and ascending rami, mandible body, or mentis.

Grade II: Involvement of bilateral maxillary tuberosities (in addition to grade I lesions) and diffuse mandibular involvement.

Grade III: Massive involvement of entire maxilla and mandible, except the condyles.

Grade IV: Involvement of both jaws, including the condyles.

The present case was presented with cherubism, hereditary gingival fibromatosis, mental retardation, and epilepsy features suggestive of Ramon's syndrome as stated by Israeli Oral surgeon Yochanan Ramon in 1967. Ramon et al described two siblings with cherubism (maxillary fibrous dysplasia), gingival fibromatosis, epilepsy, mental deficiency, hypertrichosis, and stunted growth (Table 1).¹⁸

Table 1: Features of Ramon's syndrome in case

Ramon syndrome	Features	Case
Head and neck	Cherubism, radiolucent lesions of mandible and maxilla and persistent anterior fontanelle, fibrous dysplasia.	Present
Mouth and oral structures	Gingival fibromatosis, buried teeth, narrow palate and delayed tooth eruption	Present
Nervous system	Epilepsy	Present
Growth and development	Growth and mental retardation	Present
Eyes	Optic atrophy	Present
Ears	Hearing loss	Present
Bone and joint	Juvenile rheumatoid arthritis	Absent
Skin	Vascular lesions	Absent
Skin appendages	Hypertrichosis	Absent
Endocrine system	Diabetes mellitus	Absent
Heredity	Familial occurrence in children of consanguineous parents—autosomal recessive.	Absent

De Pina-Neto et al described the same disorder in four individuals in Brazilian kindred. The features were identical to the cases as reported by Ramon et al except that three of the four patients also had juvenile rheumatoid arthritis, which Pena-Neto et al suggested should be considered as a part of the syndrome.¹⁵

Parkin and Law¹⁹ reported follow-up of two siblings with Ramon's syndrome, originally described by Pridmore et al. Both had anomalous pale optic disks and retinal abnormalities, including pigmentary retinal changes in one sibling. In addition, both siblings had bilateral anterior chamber eye anomalies (Axenfeld anomaly), not previously described in Ramon's syndrome. The authors suggested that ocular abnormalities might be another feature of this syndrome.

Conditions like craniofacial fibrous dysplasia, brown tumor and familial gigantiform cementoma may be considered for differential diagnosis of cherubism and they present with similar radiographic features as cherubism.

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