Case study

Cranio-metaphyseal Dysplasia: A review and novel oral manifestation

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ABSTRACT

Cranio-metaphyseal Dysplasia (CMD) is a sclerosing osseous dysplasia characterised by hyperostosis of craniofacial and long bones, resulting in distortion and cranial nerve palsies.

We present a case report on the management of a 63 year old female with Cranio-metaphyseal Dysplasia. This report describes an additional clinical manifestation of hypercementosis, which although well recognised in other sclerosing osseous dysplasias, is not reported in the literature for Cranio-metaphyseal Dysplasia. We discuss established *in vivo* studies in mice which link the genetic mutations found in Cranio-metaphyseal Dysplasia to hypercementosis, and how this report describes the same manifestation in humans.

This novel finding can aid the clinician in the management of patients with Cranio-metaphyseal Dysplasia, and complications that can arise in dentoalveolar surgery.

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1. Background

Cranio-metaphyseal Dysplasia (CMD) was first described in 1954 by Jackson et al, as a hereditary bone disease defined by metaphyseal widening of the tubular bones and bony overgrowth of the facial and skull bones.¹ Historically CMD had been confused with other sclerosing osseous conditions until research by Gorlin et al. in 1969, which helped establish a new classification of tubular bone disorders.²

There are only 105 cases of CMD accessible in recent literature, with the dental manifestations seldom reported.

2. Genetics

The genetic mutations in CMD produce a regulatory dysfunction of osteoclasts resulting in increased bone deposition and hyperostosis.^{3,4,5}

The autosomal dominant form of CMD identifies a mutation mapped to chromosome 5p15.2–p14.1 within a region harbouring the progressive ankylosis protein (ANK)^{6,7}.

ANK mutations entail the loss of function or expression of ANK protein and activity in the plasma membrane, as a result of aberrant intracellular protein trafficking.⁸ Mutations of ANK inhibit complex formation with skeletal inorganic pyrophosphate

(PPi), leading to defective osteoclastic activity and bone remodeling, resulting in increased bone density.³

The autosomal recessive form of CMD is rare and associated with more severe clinical manifestations. It has been mapped to chromosome 6q21–22.⁶

3. Genetics and hypercementosis

ANK is also recognised as an important protein in the development of teeth and formation of acellular cementum⁹. Studies in mice show that ‘knocking out’ the gene encoding ANK causes a significant increase in the volume of acellular cementum deposition during tooth development compared with normal controls.⁹

Without ANK, the negative feedback regulation of acellular cementum deposition is absent, resulting in hypercementosis. One study has described ANK mutant mice to have a significant increase in the formation of acellular cementum, whilst the other dental tissues remain unaffected.^{9,10,11}

The relationship between ANK and PPi is readily discussed in the literature, with emphasis on the importance of PPi in the mechanism controlling cementogenesis. It is suggested that a deficiency in PPi will result in increased cementum formation.^{7,9,10}

4. Clinical features

Clinical features of CMD including paranasal bossing, flattening of the nasal bridge and ocular hypertelorism³. Hyperostosis of the skull can cause narrowing of the cranial foramina, resulting in

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compression of the cranial nerves with consequent facial palsy, visual disturbances and conductive hearing loss.^{3,12} Affected individuals present with a prognathic mandible, making them likely candidates for orthodontic treatment and orthognathic surgery.^{3,12}

5. Radiographic features

The skull and craniofacial region have the most significant radiographic change with generalised thickening and sclerosis of the skull vault, with malformation and obliteration of the paranasal sinuses.¹³

Overall the skeleton (with the exception of the ribs, spine and pelvis) shows increased radiological density of the tubular bones, with progressive thinning of the cortex, widening of the medulla and splaying of the metaphyses (described as an *Erlenmeyer Flask* deformity).^{13,14}

6. Medical and surgical management

Current medical management is experimental, although is largely centered on calcium homeostasis given that hypocalcaemia and hypophosphataemia associated with secondary hyperparathyroidism have been described in CMD. Calcitriol in combination with a low calcium diet has shown improvement in facial paralysis and reduction of skull density in infancy.^{3,15}

Surgery can prove challenging and even life threatening in cases of foramen magnum decompression. Surgical intervention is largely palliative and long term follow up is essential due to rapid post surgical bony regrowth.

7. Case report

This report discusses the case of 63 year old female who presented to Luton and Dunstable University Hospital Oral and Maxillofacial Surgery Department with a history of pain and recurrent swellings associated with the upper left posterior teeth. The patient had endodontic treatment of both the upper left first and second premolars and subsequent apicectomy and retrograde root filling of both teeth prior to referral.

7.1. Medical history

The patient's medical history revealed an Autosomal Dominant form of Craniometaphyseal Dysplasia. The clinical manifestations of her condition were mild although she had required reductive surgery to correct facial proportions as a young adult.

7.2. Examination

A draining sinus was noted buccal to the upper left first molar and second premolar, both of which were heavily restored. Both teeth had a negative response to vitality testing.

7.3. Radiographic examination

Radiographic examination (Fig. 1a and b) revealed the upper left premolars to have periapical radiolucencies associated with the root apices, and evidence of endodontic treatment, apicectomy and retrograde root filling. The upper left first molar had a 2.5 × 2.5 cm radiopacity associated with the roots. Partial obliteration of the left maxillary antrum was also noted. There were several teeth with radiopacities of variable size associated with their root apices.

Fig. 1. a) Intraoral periapical radiograph of the 23,24,25,26 revealing gross hypercementosis of 26. b) Orthopantomogram revealing multiple periapical radiopacities associated with several teeth, and partial bony obliteration of the left maxillary antrum.

7.4. Diagnosis

Differential diagnoses of these radiopacities included localised idiopathic hypercementosis, but most likely seemed to be a manifestation of CMD.

7.5. Treatment

Whilst initial clinical examination had suggested the source of infection to be related to the endodontically treated premolars, examination under general anaesthetic revealed a sinus tract traceable to the roots of the upper left first molar tooth, which were indistinguishable from both each other and the surrounding alveolar bone. The tooth was surgically removed and biopsies of the hard and soft tissues sent for histopathological analysis (Fig. 2).

Fig. 2. Grossly hypercementosed upper left first molar following surgical extraction.

Fig. 3. Histopathology (x100 μ m magnification) showing abnormal thickening of acellular cementum with the presence of lacunae and canaliculi in keeping with cementum hypertrophy. There is no evidence of the cementum-dentine junction and no bone present.

The soft tissue lesion showed granulation tissue consisting of chronic inflammatory cells including plasma cells and lymphocytes. The histopathology report of the hard tissue showed abnormal thickening of acellular cementum in keeping with cementum hypertrophy, with no evidence of the cementum-dentine junction. The report concludes that the features are consistent with the clinical diagnosis of hypercementosis (Fig. 3).

The patient was reviewed one week and six months post extraction with no complications reported.

8. Discussion

Whilst a commonly accepted feature of other sclerosing osseous dysplasias, there are no reports of hypercementosis in patients affected by CMD. Our clinical data and histological report supports both genetic and in vivo studies in mice and suggest that hypercementosis should be considered an additional oral feature of CMD, a feature not yet described in humans. Reduced or absent ANK function and consequent reduced expression of PPi as a result of genetic mutations are already established genetic features of CMD. The same mutations have been demonstrated to cause an increased deposition of acellular cementum and hypercementosis

during tooth development as seen in the histopathology in this case.^{9,10,11}

This report has been constructed to develop an understanding of Craniometaphyseal Dysplasia and aid planning for dentoalveolar surgery in affected patients. A multidisciplinary approach from pre-conception with genetic counselling, to dental and craniofacial management in adulthood is essential.

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